Expert Report

Prepared by
Dr. Edward C. Ketyer, M.D., F.A.A.P.

In the matter of:

Substantive Validity Challenge to Penn Township Zoning Ordinance, *Protect PT v. Penn Township Zoning Hearing Board v. Huntley & Huntley Energy Exploration, LLC and Apex Energy (PA), LLC*, Case No. 3499 of 2017, Westmoreland County Court of Common Pleas

Prepared for
Hamilton Law, LLC
PO Box 40257
Pittsburgh, PA 15201

October 20, 2017

Table of Contents

I. Expert Credentials (see attached CV in Appendix A)

Pediatrician for 27+ years with special interests in preventative medicine, and how nutrition and the environment affect health; member of AAP Council on Environmental Health; consultant to SWPA-EHP; member of Air Quality Collaborative (Allegheny County); Physicians for Social Responsibility - PA board member; Clinical Assistant Professor of Pediatrics at University of Pittsburgh SOM.

II. Introduction

Humanity today finds itself at an existential crossroads. After two-a-half centuries of increasing global industrialization, we approach an inevitable obstacle to continuing business-as-usual: clear evidence of a global climate crisis. The other fact we must all face is based in a simple physical reality: Earth is a closed system; what happens here stays here.

Here are some other facts that we know: Industries that extract and burn, in great quantities, carbon-based fossil fuels (coal, oil, natural gas) emit prodigious quantities of health-harming particles and chemicals into the atmosphere. These emissions — as we know from decades of global, evidence-based, peer-reviewed, scientific research and medical practice — make people sick, diminish their health and the quality of their lives, and kill them prematurely. We also know that while some people are more vulnerable to the effects of pollution in the air they breathe, the water they drink, and the food they eat — pregnant women and children, the elderly, those who live in poverty, people with pre-existing medical conditions — no one person is immune from adverse health impacts of pollution.

We also know what emissions come from unconventional natural gas development (a.k.a. “fracking”), where along the chain of infrastructure they come from, what symptoms of people living in proximity to these activities are experiencing, and what diseases are developing or being exacerbated by these emissions into the air we all breathe, the water we all drink and bathe in, and the soil in which we grow our food and on which our children play.

This is why the Pennsylvania Medical Society, which represents 16,000 Pennsylvania physicians and medical students, has come together and called for a moratorium on unconventional natural gas development. It adversely affects human health, and especially the health of children. We know that industrial air pollution, like the kind emitted from shale gas infrastructure and during consumption of methane, means more asthma in children, more chronic lung disease and heart disease in adults, more cancer in both adults and children, and, as some recent peer-reviewed studies have shown, perhaps more autism, ADHD, and other neurodevelopment problems in children.

Airborne emissions occur at every stage of UNGD. The enormous volume of heavy diesel trucks passing along our highways, county roads, and through our communities means more of toxic

particulate matter, more volatile organic compounds and polycyclic aromatic hydrocarbons, more carbon monoxide, carbon dioxide, nitrogen oxides and ozone. Science continues to tell us that each and every one of these emissions makes people sick — especially children. These toxic emissions are released inadvertently, or out of necessity, at well pads, during pipeline construction and maintenance, at compressor stations, and at processing facilities. Also, let's remember that a healthy percentage of the methane (2-8%) produced by this industry is leaked inadvertently, and vented and flared off *by design* into the atmosphere. Methane, as you know, is a potent heat-trapping, greenhouse gas — 86 times more potent than CO2 over a 20-year timeframe, and 20 times more potent over a hundred year span.

Toxics generated by the oil and gas industry also spill onto the ground and make their way into ground water aquifers as well as into rivers and streams. With air pollution, what goes up comes down. With spills, what goes down (into the well) — a liquid concoction of millions of gallons of fresh water that can never be allowed to return to the Earth's natural water cycle), chemicals that are not publicly disclosed, and sand as a proppant — comes back up in the form of "flowback", which is water contaminated with the chemicals used in fracking (many of which are known to affect pregnancy outcomes, cause birth defects, cancer, and other human diseases). Also in that "flowback" are toxic heavy metals such as arsenic and lead, and naturally-occurring radioactive materials like uranium, thorium, and radium, which come from Earth's crust.

My testimony today, drawing from previous presentations and testimony, will address the peer-reviewed consensus regarding health risks associated with UNGD.

III. Health effects/studies

A. Introduction — Before we consider the growing body of scientific and medical evidence, and the abundant wisdom that comes from common sense, we should remember that:

No credible scientist ever said, "Exposure to air pollution is safe for human health." No credible physician ever said, "Breathing air polluted with particulate matter and VOCs is not harmful." No credible pulmonologist ever said, "Ground-level ozone affects every human's lung function EXCEPT YOURS." No credible cardiologist ever said, "Air pollution from natural gas production is less harmful to your heart than emissions from coal." (Or "putting a filter on a Camel cigarette makes smoking okay.") No credible psychiatrist ever said, "It's just another gas well. Relax." No credible pediatrician ever said to a concerned mother, "Air pollution is fine — your kids won't suffer."

Numerous peer-reviewed studies however have demonstrated a link between air pollution and public health, and particularly on those most vulnerable in the population. Air pollution has been shown to be a trigger for childhood asthma (a diagnosis which is prevalent in at least 8-9% of American children), and a factor in the premature development of coronary artery disease (heart attacks) and cerebrovascular disease (strokes). It has also been shown to cause complications during pregnancy (increases in premature births and infant mortality) and to be associated with

chronic — and sometimes terminal — illness, disease, and premature death. Simply put, adverse health effects from the components of air pollution emitted by fossil fuel sources occur from cradle to grave.

B. Why Are Children Most Susceptible to Harms from Air Pollution?

As a practicing pediatrician, I believe it is important for you to understand why children are at higher risk for experiencing the harmful effects of pollution. Children are not little adults. How they come into contact with dangerous pollutants and how their immature organs and immune systems handle these pollutants is far different from adults. Children's bodies are especially susceptible to toxic chemical actions because of their size and because of the normal processes of growth and development.

Children are not like adults:

- Per unit body weight, they breathe more air, drink more water, and eat more food than adults.
- They spend more time playing outdoors.
- Their play tends to be closer to where industrial fallout occurs — in grass, dirt, and bodies of water — and, thus, they are often exposed to higher doses of pollutants.
- Unlike full-size adults, children (including fetuses and infants) undergo continuous anatomic and physiologic growth and development. Normal processes of growth and development such as cell division, tissue differentiation, and organ migration can be disturbed and interrupted, resulting in birth defects, neurocognitive deficits, and various medical problems that are unique to — or more severe in — children. Asthma is just one of these.
- Children have a longer "shelf-life" than adults. That is, there is more time for a child to present with clinical manifestations resulting from toxic exposures than an adult exposed at the same time. Children have longer to live than their parents and grandparents; it's only fair that we acknowledge that.

Our children — the best and most important things each of us has ever made and will ever make — are the most vulnerable people among us. Pollution which emanates from heavy industry is bad enough for adults (air pollution is a major contributor to heart disease, lung disease, and cancer) but it's worse for our kids. This is what science has been telling us for a long, long time.

C. Health Effects of Air Pollution in Children

1. Respiratory problems:

> Air pollution increases their risk of developing asthma.

> Air pollution worsens symptoms of existing asthma, viral-induced wheezing, chronic lung disease in premature infants (BPD), acute bronchiolitis in infants, cystic fibrosis, and other respiratory tract conditions.

> Air pollution increases the risk of developing other lower airway diseases and infections,including bronchiolitis, pneumonia, chronic obstructive airway disease (COPD), and silicosis.

> Air pollution increases the risk of upper respiratory complications such as non-allergic rhinitis (runny nose) and conjunctivitis (red eyes), pharyngitis (sore throat), sinusitis, and otitis media (ear infections).

A recent (not-yet-published) study from my colleague, Dr. Deborah Gentile, revealed that the risk of a school-aged child living in Pittsburgh and developing asthma is nearly three times the national average because of high particulate matter and ozone levels contributing to the region's poor air quality

http://www.nextpittsburgh.com/latest-news/asthma-is-an-epidemic-among-pittsburgh-schoolchildren-how-can-communities-breathe-easier/

2. Childhood Obesity

While the effects on the respiratory system are well documented, others are investigating effects that one may not anticipate. *Rundle, et al* reported in the *American Journal of Epidemiology* in 2011 the association of childhood obesity and maternal exposure to air pollution during pregnancy — specifically exposure to polycyclic aromatic hydrocarbons which are emitted in abundance during the natural gas extraction process.

Rundle, A., et al — Association of Childhood Obesity With Maternal Exposure to Ambient Air Polycyclic Aromatic Hydrocarbons During Pregnancy (*American Journal of Epidemiology* June 2012 School of Public Health, Columbia University)
http://aje.oxfordjournals.org/content/175/11/1163

3. Neurologic and Neurodevelopmental Disorders/Autism/ADHD:

A 2005 landmark study examining umbilical cord blood of newborn babies described neurologic/neurodevelopmental/behavioral impacts of pollution in children and delivered news that should unsettle everyone: babies are being born "pre-polluted". In 10 of these "pre-polluted"

babies, a total of 287 different chemicals were found, including 180 that cause cancer in humans or animals, 217 that are known to be toxic to the brain and nervous system, and 208 that are known to cause birth defects or abnormal development in animal tests.

Environmental Working Group — Body Burden: The Pollution in Newborns
(*Environmental Working Group* July 2005)
http://www.ewg.org/research/body-burden-pollution-newborns

> Lower IQ: A December 2014 study, published in the online journal *PLOS ONE*, demonstrated decreased child IQ associated with maternal prenatal exposure to phthalates.
(Phthalates are chemicals used in the production of plastics and are ubiquitous in the environment.)

Factor-Litvak, P., et al — Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years (*PLOS ONE* December 2014 Columbia University School of Public Health)
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114003

> Autism: Several studies have begun to associate air pollution with Autism Spectrum Disorder (ASD). In March 2015, a study from the Harvard School of Public Health and Harvard Medical School involving over 100,000 participants concluded that a higher maternal exposure to PM2.5 during pregnancy, in particular the third trimester, was associated with greater odds of her child having ASD.

Raz, R., et al — Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case–Control Analysis within the Nurses' Health Study II Cohort (*Environmental Health Perspectives* March 2015 Harvard School of Public Health/Harvard Medical School)
http://ehp.niehs.nih.gov/1408133/

A January 2014 study published in the journal *Epidemiology* was able to link the interaction of a specific gene and air pollutant exposure to an increased risk of autism.

Volk, H., et al — Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. (*Epidemiology* January 2014 University of Southern California)
http://www.ncbi.nlm.nih.gov/pubmed/24240654

In 2016, researchers from the University of Pittsburgh published another study linking air pollution and autism. For this study, researchers at the University of Pittsburgh conducted a population-based case control study in six counties in southwestern Pennsylvania, estimating the association between autism spectrum disorders and 30 known neurotoxicants. The researchers found that exposure to chromium, cyanide, styrene and other toxic air pollutants during

pregnancy and a child's early years of life increased the likelihood that a child would be diagnosed with an autism spectrum disorder.

Talbot, E., et al — The Association of National Air Toxics Assessment Exposures and the Risk of Childhood Autism Spectrum Disorder: A Case Control Study (*American Association for Aerosol Research* October 2014 University of Pittsburgh)
http://aaarabstracts.com/2014/viewabstract.php?pid=599

Finally, a 2013 study in *JAMA Psychiatry* showed that exposure to traffic-related air pollution (in other words, particulate matter, benzene, carbon monoxide, carbon dioxide, nitrogen oxides) during pregnancy and during the first year of life was associated with autism.

Volk, H., et al — Traffic-Related Air Pollution, Particulate Matter, and Autism (*JAMA Psychiatry* January 2013 University of Southern California)
http://archpsyc.jamanetwork.com/article.aspx?articleid=1393589

> ADHD: *Perera et al.* elegantly demonstrated (by evaluating umbilical cord blood at birth) that prenatal exposure to polycyclic aromatic hydrocarbons — which are widespread when air is polluted primarily through the burning of fossil fuels and are known carcinogens, mutagens, and teratogens — may play a role in the development of Attention Deficit/Hyperactivity Disorder.

Perera, F., et al — Early-Life Exposure to Polycyclic Aromatic Hydrocarbons and ADHD Behavior Problems (*PLOS ONE* November 2014 Columbia University)
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0111670#abstract0

D. Health Effects Associated with Unconventional Natural Gas Extraction

As scientists and public health professionals continue to research and learn more about UNGD, a number of studies have documented adverse health effects associated with unconventional natural gas extraction.

1. Self-Reported Symptoms: A comprehensive study by *Steinzor et al*. published in 2013 investigated self-reported health symptoms of persons residing near shale gas sites in Pennsylvania. The study reported on prevalent self-reported health symptoms that went beyond the respiratory symptoms mentioned previously, and included increased fatigue, severe headaches muscle aches and weakness, anxiety and depression, dizziness and nausea, memory problems, skin irritations, sleep disturbances, and more.

The study reports that these symptoms were consistent with exposures to the types of chemicals found in air tests performed during the time of the survey and in proximity to gas sites. The air tests together detected 19 chemicals that are known to cause sinus, skin, ear/nose/throat, and neurological symptoms, 17 that may affect eyes and vision, and 16 that may induce behavioral effects; as well as 11 that have been associated with liver damage, nine with kidney damage, and

eight with stomach and other digestive problems. In addition, the brain and nervous system may be affected by five of the volatile organic compounds (VOCs) detected; the cardiac system by five; muscles by two; and blood cells by two.

Steinzor, N., Subra, W., et al — Investigating Links Between Shale Gas Development And Health Impacts Through A Community Survey Project In Pennsylvania (*Scientific Solutions* Earthworks 2013)
https://www.earthworksaction.org/files/publications/SteinzorSubraSumiShaleGasHealthImpacts2013.pdf

Rabinowitz et al. surveyed residents in Washington County in a 2013 study published in the Journal *Environmental Health Perspectives*. The aim of the study was to assess the relationship between household proximity to natural gas wells and reported health symptoms. At the time of the study, there were over 600 active unconventional natural gas wells in the county. The researchers were able to associate proximity to natural gas wells and the prevalence of not only respiratory symptoms, but also skin rashes.

Rabinowitz, P., et al — Proximity to Natural Gas Wells and Reported Health Status: Results of a Household Survey in Washington County, Pennsylvania
(*Environmental Health Perspectives* January 2015 Yale University)
http://ehp.niehs.nih.gov/1307732/

Researchers from Pennsylvania's Geisinger Health System and Johns Hopkins University found that Pennsylvania residents with the highest exposure to active natural gas wells operated by the hydraulic fracturing ("fracking") industry are nearly twice as likely to suffer from a combination of migraine headaches, chronic nasal and sinus symptoms, and severe fatigue.

The understanding is that development of oil and gas wells generates toxic air pollution, which, as we've just seen, provokes nasal and sinus symptoms. This type of drilling also produces stressors such as odors, noise, bright lights and heavy truck traffic. Any of these stressors could increase the risk of symptoms. Migraine headaches, for example, are known to be triggered by odors in some individuals.

Tustin, A., et al (*Environmental Health Perspectives* - Online)
https://www.sciencedaily.com/releases/2016/08/160825084623.htm

In September 2017, researchers with the SWPA Environmental Health Project confirmed similar reported health symptoms in people living in proximity to shale gas infrastructure. The top 10 symptoms reported were sleep disruption, headache, throat irritation, stress/anxiety, cough, shortness of breath, sinus problems, fatigue, nausea, and wheezing.

Weinberger, B. et al — Health symptoms in residents living near shale gas activity: A retrospective record review from the Environmental Health Project
http://www.sciencedirect.com/science/article/pii/S2211335517301353?via%3Dihub

2. Complications of Birth/Abnormal Birth Outcomes: In December 2014, *Webb, et a*l published an extensive review titled: "Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations" in the journal *Reviews on Environmental Health.*

Developmental health effects that were present included:

> Impaired fetal growth
> Low birth weight
> Birth defects

Reproductive health effects that were observed included:

> Infertility
> Miscarriage
> Preterm births (prematurity)

These conditions have been associated with chemicals and compounds that occur in every stage of natural gas development: volatile organic compounds (VOC's) such as the BTEX compounds (benzene, toluene, ethyl benzene, and xylene) and formaldehyde, and the heavy metals arsenic, cadmium, and lead.

A postulated mechanism of action for these conditions has been getting a lot of attention in recent years: that these (and other chemicals) act as "endocrine disruptors." Endocrine disruptors interfere with the synthesis, secretion, transport, binding, actions, or elimination of natural hormones. They are known to cause:

> Birth deformities in the embryo (examples are the well-known effects of DES and Thalidomide from generations past).
> Cancers — particularly in organs especially sensitive to hormones such as in the breast, prostate, and thyroid gland.
> Neurodevelopment disorders — including learning disabilities and ADHD.
> Embryonic disorders of sexual development — including feminization and androgen excess syndromes.

The *Webb* paper suggests that even tiny doses of benzene, toluene and other chemicals released during the various phases of oil and natural gas production, including hydraulic fracturing, could pose serious health risks -- especially to developing fetuses, babies and young children. Among the more than 750 chemicals known to be used in hydraulic fracturing, a significant subset (at least 130) may carry the potential to disturb the natural hormone messengers responsible for critical processes such as sleep, metabolism, growth, and reproduction. Even in very small concentrations, these endocrine disruptors have been shown capable of derailing normal brain

and sexual development, diminishing the immune system's ability to fight disease, cause certain cancers, and other effects.

Webb, E., et al — Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations (*Reviews on Environmental Health* December 2014)
http://www.degruyter.com/view/j/reveh.2014.29.issue-4/reveh-2014-0057/reveh-2014-0057.xml?format=INT

A 2016 Pennsylvania study, published in the journal *Epidemiology*, demonstrated an association between proximity of women living near natural gas operations and two adverse birth outcomes: Preterm (premature) births and higher rates of high risk pregnancies (pregnancy-induced hypertension (pre-eclampsia), asthma, maternal obesity).

Casey, J., et al —Unconventional Natural Gas Development and Birth Outcomes in Pennsylvania, USA (*Epidemiology)*
http://journals.lww.com/epidem/Citation/2016/03000/Unconventional_Natural_Gas_Development_and_Birth.2.aspx

An analysis of birth records from researchers at the University of Pittsburgh Graduate School of Public Health in 2015 found that pregnant women living close to a high density of natural gas wells drilled with hydraulic fracturing were more likely to have babies with lower birth weights than women living farther from such wells.

"Developing fetuses are particularly sensitive to the effects of environmental pollutants," said co-author Dr. Bruce Pitt. "We know that fine particulate air pollution, exposure to heavy metals and benzene, and maternal stress all are associated with lower birth weight."

Stacy, S., et al — Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania (*PLOS ONE* June 2015 — Univ. of Pittsburgh)
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0126425

A 2015 study from Children's Hospital of Cincinnati found exposure to high levels of fine particulate air pollution (PM2.5) in the third trimester of pregnancy was associated with a 42% increased risk of miscarriage and fetal death (stillbirth).

DeFranco, E., et al — Air Pollution and Stillbirth Risk: Exposure to Airborne Particulate Matter during Pregnancy Is Associated with Fetal Death (*PLOS ONE* March 2015 Children's Hospital of Cincinnati/University of Cincinnati)
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0120594

The same researchers from Cincinnati also found that exposure to high levels of small particle air pollution (PM2.5) was associated with an 19% increased risk of preterm birth — before 37 weeks of pregnancy — with exposure in the third trimester accounting for the highest risk.

DeFranco, E., et al — Exposure to airborne particulate matter during pregnancy is associated with preterm birth: a population-based cohort study (Environmental Health — January 2016 Children's Hospital of Cincinnati/Univ. of Cincinnati)
http://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0094-3

3. Birth Defects — Congenital Heart Disease, Spina Bifida: In a study that has gotten a lot of attention from the pediatric community in 2014, *McKenzie, et al*. studied birth outcomes and maternal residential proximity (within ten miles) to natural gas wells in Colorado and found these disturbing findings: The closer that pregnant mothers lived to natural gas wells, the higher the incidence of congenital heart diseases. There was also a possible correlation of proximity and neural tube defects such as spina bifida. Birth defects are a leading cause of neonatal mortality and natural gas development emits several potential teratogens. The study also indicated a positive relationship between increased density of gas wells and mothers who gave birth to children with certain defects, with one of the most likely culprits being benzene emissions. It is important to note that these birth defects occurred when mothers lived within a radius of 10 miles from natural gas wells.

McKenzie, L., et al — Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado (*Environmental Health Perspectives* April 2014)
http://ehp.niehs.nih.gov/1306722/

4. Asthma: Another study from the folks at Geisinger and Johns Hopkins that was published in the *Journal of the American Medical Association Internal Medicine* received a great deal of attention in the media after showing that people who lived near a large number of active natural gas wells were 1.5 to 4 times more likely to suffer from asthma attacks compared to those who lived farther away. The risk also showed this association between asthma exacerbations and proximity to activity in all four phases of well development — pad preparation, drilling, stimulation (fracking), and production. The authors of the study point to air pollution emitted during the totality of unconventional natural gas operations and stress as the main culprits for worsening asthma symptoms in these Pennsylvania residents.

Rasmussen, S., et al — Association Between Unconventional Natural Gas Development in the Marcellus Shale and Asthma Exacerbations (*JAMA Internal Medicine*)
http://archinte.jamanetwork.com/article.aspx?articleid=2534153

5. Lung cancer: Geisinger and Hopkins researchers also found that radon levels in buildings near unconventional natural gas development in Pennsylvania are higher than those in other

areas of the state, suggesting that hydraulic fracturing has opened up new pathways for the carcinogenic gas to enter people's homes.

Radon is the second leading cause of lung cancer worldwide next to tobacco. Tobacco and radon occurring in tandem is an especially dangerous and deadly combination. Children who are exposed to secondhand tobacco smoke in their homes as well as to radon may be extremely vulnerable.

Casey, J., et al — Predictors of Indoor Radon Concentrations in Pennsylvania, 1989–2013 (*Environmental Health Perspectives* April 2015)
http://ehp.niehs.nih.gov/1409014/

6. Hospitalizations: Hospitalizations for heart conditions were about 27% higher over five years among residents who lived in zip codes with more wells than among those whose zip codes had the least.

Neurology admissions also increased significantly for zip codes with more wells.

The study's senior author at the University of Pennsylvania speculated that more air pollution and higher environmental stress could have caused the cardiology increases.

> "Our guess is that the numbers of big trucks," he said, caused a "tremendous increase in diesel exhaust fumes as well as ozone." Noise may have disrupted sleep, leading to rising cases of hypertension and heart disease, the author said.

Jemielita, T., et al — Unconventional Gas and Oil Drilling Is Associated with Increased Hospital Utilization Rates (*PLOS ONE* July 2015 University of Pennsylvania)
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0131093

7. Mental Health: Mental illness is an adverse side effect of environmental degradation and destruction, as well as pollution. The psychologic and behavioral fallout from natural gas extraction is not trivial. As we've already seen, ADHD has been associated with exposure to air pollution. Mental health disorders — especially anxiety and depression — have also been shown to be associated with pollution exposure.

In 2013, a study from the University of Pittsburgh reported that the most common concern cited by 76% of residents living in proximity to natural gas wells was "stress".

> UPMC reported: "Among the leading causes of stress reported by the participants were feelings of being taken advantage of, having their concerns and complaints ignored, and being denied information or misled."

The study reported, importantly, that these effects were not temporary:

> "Reported health impacts persist and increase over time, even after the initial drilling activity subsides."

Ferrar, et al — Assessment and longitudinal analysis of health impacts and stressors perceived to result from unconventional shale gas development in the Marcellus Shale region (*International Journal of Occupational and Environmental Health* November 2013 University of Pittsburgh)
http://www.tandfonline.com/doi/full/10.1179/2049396713Y.0000000024

Stress can be caused by a number of factors associated with the gas industry:

> > Noise: Noise associated with gas operations, such as drilling, hydraulic fracturing, flaring, regular pipeline maintenance (via the "pig launcher"), and truck traffic, keeps people awake at night and on edge during the day. Sleep deprivation is a known and powerful trigger of anxiety and depression — this is well-documented in the pediatric literature.
>
> > Odors: The sheer volume of diesel fumes produced throughout the many-year life cycle of a natural gas well creates a pervasive industrial stench. Other fumes produced during this heavy industrial process add to the stench. Air is not supposed to smell like anything. When it does — and your brain decides it's a bad smell — it's already past your olfactory bulbs and into your lungs and bloodstream.
>
> > Traffic: Residents have testified in townships that allow unconventional natural gas extraction about being terrified to drive on the same narrow country roads as huge trucks involved in the process. Roads are chewed up. Large truck traffic on residential streets, main streets, and the interstate increases. The fear appears to be validated by the report by the Multi-State Shale Collaborative, which found that there is a statistically significant increase of truck-related traffic fatalities in communities with natural gas drilling.
>
> > Crime: This same study (The Relationship of Drilling to Crime, Traffic Fatalities, STD's, and Rent in PA, WVa, and Ohio from 2005-2012) also concluded:
>
> > > "There was a statistically significant increase in violent crime of 17.7% in high-drilling counties… [Washington and Greene Counties included]."
> >
> > > "We observed a statistically significant increase in property crime of 10.8% in high-drilling counties."
> >
> > > Also increased in this report: In high-drilling counties, including Washington and Greene Counties, drug and alcohol abuse (by 48%), sexually-transmitted diseases

(Chlamydia by 24-27%; interestingly, gonorrhea's incidence has increased across the entire state, irrespective of natural gas drilling.); and "truck-involved" motor vehicle fatalities (by 27.8%).

Smalldone, et al — Sleepless in America: Inadequate Sleep and Relationships to Health and Well-being of Our Nation's Children
http://pediatrics.aappublications.org/content/119/Supplement_1/S29?sid=c9a19cb1-cb18-48eb-a044-653344aef48d

Owens, J., Insufficient Sleep in Adolescents and Young Adults: An Update on Causes and Consequences. Adolescent Sleep Working Group, AAP Committee on Adolescence.
http://pediatrics.aappublications.org/content/134/3/e921?sid=c9a19cb1-cb18-48eb-a044-653344aef48d

Price, M., et al —The Shale Tipping Point: The Relationship of Drilling to Crime, Traffic Fatalities, STDs, and Rents in Pennsylvania, West Virginia, and Ohio (*The Multi-State Shale Research Collaborative* December 2014)
http://www.multistateshale.org/shale-tipping-point

8. Pennsylvania Air Toxics Inventory from UNGD

As scientific research continues — much of it conducted in communities in Pennsylvania — evidence continues to mount and point to threats to public health and safety posed by the heavy industrial process of UNGD.

In 2016, the Pennsylvania Department of Environmental Protection released the Air Inventory Data Report for 2014 — data which is derived from information provided by the industry. The report shows that air pollutants emitted at all phases of UNG development have increased at all points of natural gas operations — from the clearing of land to create well pads, to the drilling and the fracking that brings up methane and liquid fuels from deep down in Earth's crust, to the transportation of the products gathered at the well site to processing and export facilities via diesel trucks, trains, and pipelines, with additional and significant emissions coming from other infrastructure like pig launchers, compressor stations, giant flowback evaporation pits, and landfills.

Emissions of:

— Sulfur dioxide — a respiratory toxic — increased by 40% between 2013 and 2014.

— Nitrogen oxides — a main component of ozone and smog (which are respiratory toxics) — increased by 18%.

— Volatile Organic Compounds (VOC's) — the other main component of ozone, are respiratory toxics, liver and kidney toxics, neurotoxics, and carcinogens — increased by 25%

— Fine particulate matter (PM2.5) — a major component of smog and a cardiorespiratory toxic and carcinogen — increased by 25%.

— Carbon monoxide — emitted in abundance by diesel and gas-powered engines present at all stages of this heavy industrial process and poisonous to every human body — increased by 19%.

— Carbon dioxide and methane emissions — the two main greenhouse gases responsible for global warming and climate change — both increased in 2014. (CO2 by nearly 20%.)

Pennsylvania Department of Environmental Protection — 2015 Oil and Gas Report
http://www.elibrary.dep.state.pa.us/dsweb/Get/Document-113887/8000-RE-DEP4621.pdf

PA-DEP Air Inventory Data
http://www.dep.pa.gov/Business/Air/BAQ/BusinessTopics/Emission/Pages/Marcellus-Inventory.aspx

IV. Conclusion

In my opinion, the findings from these and other studies need to be considered seriously when evaluating siting natural gas facilities near where children live, learn, and play. These studies have passed peer review, which is the highest level of scientific evaluation available. The adverse effects documented by these reports tend to be especially hazardous for individuals with health conditions that make them susceptible to air toxins, such as pregnant women, children with asthma, and people with other chronic health conditions.

The scientific evidence that unconventional natural gas extraction endangers health and safety is substantial and growing. These studies and reports inform us of the hazards to human health this heavy industrial process has on all of us, but especially, our children. Their fast-growing and rapidly developing bodies are susceptible to adverse health effects from exposure to particulate matter (PM2.5), ground-level ozone, volatile organic compounds (VOCs, like benzene, a known carcinogen), polycyclic aromatic hydrocarbons (which act as endocrine-disrupting chemicals), carbon monoxide, radon, silica particles, naturally-occurring radioactive materials (NORMs), heavy metals, etc. I should point out that pregnant women are also extremely vulnerable to these pollutants. Miscarriages, pregnancies ending before term, and birth defects have all been documented in Pennsylvania.

Finally, as the pros and cons (adverse health effects) of approving unconventional natural gas development around where children live, learn, and play are considered, understand that the very fabric of this community will be stressed, perhaps frayed, maybe even torn apart, as it has been in so many other communities in the Marcellus Shale region.

/s/ Edward C. Ketyer

Edward C. Ketyer, M.D., F.A.A.P.
Pediatric Alliance, P.C.
Editor, *The PediaBlog*
AAP Council on Environmental Health
Southwest Pennsylvania Environmental Health Project
Physicians for Social Responsibility - Pennsylvania
Clinical Assistant Professor of Pediatrics, University of Pittsburgh School of Medicine

October 20, 2017

APPENDIX A: PROFESSIONAL CV

PEDIATRIC ALLIANCE, P.C.
CHARTIERS/MCMURRAY DIVISION

EDWARD C. KETYER, M.D., F.A.A.P.

DOB: December 8, 1959
BIRTHPLACE: New York, N.Y.
ADDRESS: 102 Meadowvue Court
Venetia, PA 15367
CONTACT: 724-255-7440 /// ecketyer@gmail.com

EDUCATION:

High School: Columbia High School 1975-1978
Maplewood NJ

Undergraduate: University of Vermont 1978-1982
Burlington, VT.
(Grad. 5/82 — B.A. Zoology)

Medical School: Far Eastern University 1982-1985
Manila, Philippines

Medical School: Northwestern University 1985-1987
Chicago, IL.
(Grad. May 1987 — M.D.)

POST GRADUATE TRAINING: Pediatrics Resident - Children's Hospital of Pittsburgh 1987-1990.

PEDIATRIC PRACTICE: Pediatric Alliance, PC (www.pediatricalliance.com),
— Primary care pediatric practitioner — Chartiers/ McMurray Division — 1990-2016 (retired).

— Editor and principle writer, *The PediaBlog*
2012-present (www.thepediablog.com)

ACADEMIC POSITIONS: University of Pittsburgh School of Medicine
Department of Pediatrics
— Clinical Instructor of Pediatrics - 1990-1995.
— Clinical Assistant Professor of Pediatrics -

1996-present.

BOARD CERTIFICATION: American Board of Pediatrics – Initial Certification - 1990
Recertification - 1997, 2004, 2011

FORMER HOSPITAL STAFF AFFILIATIONS:

Children's Hospital of Pittsburgh
3705 Fifth Avenue
Pittsburgh, PA. 15213-2583

Magee-Womens Hospital
300 Halket Street
Pittsburgh, PA. 15213-3180

St. Clair Hospital
1000 Bower Hill Road
Pittsburgh, PA. 15243-1899

ORGANIZATION MEMBERSHIPS:

— American Academy of Pediatrics (AAP), Fellow
— AAP - Pennsylvania Chapter - 1990-present.
— AAP - Council on Environmental Health - 2013-present.

COMMITTEES:

Pediatric Alliance, P.C.
— President, Board of Directors – 1997-2004.
— Member, Board of Directors — 1996-2016.
— Member, EMR Committee (Electronic Medical Records) — 2006-2016.
— Chair, Strategic Marketing Committee — 2017-present.
— Chair, Social Media Committee — 2017- present.

Children's Hospital of Pittsburgh:
— Children's Health Network (CHN) – Board of Directors - 1995-1996
— Teaching and Education/Residency Curriculum Committee - 1995-97

Magee Women's Hospital:
— Magee Physician Hospital Organization – Board of Directors, MPHO - 1994-1996
— Membership Committee, MPHO - 1994-1996

— Strategic Planning Committee, MPHO - 1994-1996

St. Clair Hospital:

— Infection Control Committee - 1990-1992

— Pediatric Quality Improvement Committee (QIT) — 1993-2014

— Executive Committee (Department Chair) - 2010-2012

CONSULTING:

Southwest Pennsylvania Environmental Health Project (SWPA-EHP) - 2015-present. www.environmentalhealthproject.org.

PRESENTATIONS:

"Baby Basics" at Pediatric Alliance - Prenatal class for expectant parents, twice a year (1990-2016).

"Baby Basics" at St. Clair Hospital - Prenatal class for expectant parents, twice a year (1990-2016).

"Addressing Shale Health Issues in Practice"

— 3rd Annual Shale Gas Extraction and Public Health Conference presented by the League of Women Voters of Pennsylvania. November 18, 2015.

"Kids' Health in the Gas Patch"

— Three Rivers Pediatric Update, presented by Children's Hospital of Pittsburgh. May 21, 2016.

— Health and Shale Gas Development: State of the Science Conference presented by Southwest PA Environmental Health Project. June 10, 2016.

Professional testimony on behalf of residents affected by unconventional natural gas development (Transcripts available on request):

— Mt. Pleasant Township, Washington County, PA Board of Supervisors — January 7, 2015.

— Peters Township, Washington County, PA, Township Council, January 2015 (public comment).

— Ligonier Valley, Westmorland County, PA, Township Supervisors — February 17, 2015.

— Chartiers Township, Washington County, PA

Board of Supervisors — May 26, 2015.

— Mt. Pleasant Township, Planning Council — September 19, 2016.

— Public Comment on proposed ground-level ozone standard, White House Office of Management and Budget (OMB), September 24, 2015.

— "It's All We've Got: Health in a Warmer World" (Health impacts of climate change)

— March 13, 2017, University of Pittsburgh Graduate School of Public Health lecture (Prof. James Fabisiak).

— May 17, 2017, Cornerstone Care Teaching Health Center Family Medicine Residency lecture (Mt. Morris, PA).

— October 25, 2017 (upcoming), Bentleyville, PA Public Library.

— November 13, 2017 (upcoming), 5th Annual League of Women Voters Shale & Health Conference (Healthcare provider break out session.

— "Location! Location! Location! — Know Your Zip Code!" (A tour of Allegheny County, PA reveals pollution hot spots and health impacts.)

— May 3, 2017 Magee-Women's Hospital (Making The Connection: Physical Activity, Air Pollution and Asthma in the Urban Environment)

— September 8, 2017 Pittsburgh Asthma Summit

(Updated: 09/20/17)

APPENDIX B: REFERENCES

Preventive Medicine Reports 8 (2017) 112–115

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Short communication

Health symptoms in residents living near shale gas activity: A retrospective record review from the Environmental Health Project

Beth Weinberger[a,*], Lydia H. Greiner[b], Leslie Walleigh[c], David Brown[a]

[a] Southwest Pennsylvania Environmental Health Project, The Grove, 760 Chapel St., New Haven, CT 06510, United States
[b] Southwest Pennsylvania Environmental Health Project, 2001 Waterdam Plaza Suite 201, McMurray, PA 15317, United States
[c] Southwest Pennsylvania Environmental Health Project, 2001 Waterdam Plaza Suite 201, McMurray, PA 15317, United States

ARTICLE INFO

Keywords:
Hydraulic fracturing
Health
Fracking
Shale gas
Unconventional gas

ABSTRACT

Increasing evidence demonstrates an association between health symptoms and exposure to unconventional natural gas development (UNGD). The purpose of this study is to describe the health of adults in communities with intense UNGD who presented for evaluation of symptoms. Records of 135 structured health assessments conducted between February 2012 and October 2015 were reviewed retrospectively. Publicly available data were used to determine proximity to gas wells. Analysis was restricted to records of adults who lived within 1 km of a well in Pennsylvania and denied employment in the gas industry (n = 51). Symptoms in each record were reviewed by a physician. Symptoms that could be explained by pre-existing or concurrent conditions or social history and those that began or worsened prior to exposure were excluded. Exposure was calculated using date of well drilling within 1 km. The number of symptoms/participant ranged from 0 to 19 (mean = 6.2; SD = 5.1). Symptoms most commonly reported were: sleep disruption, headache, throat irritation, stress or anxiety, cough, shortness of breath, sinus problems, fatigue, nausea, and wheezing. These results are consistent with findings of prior studies using self-report without physician review. In comparison, our results are strengthened by the collection of health data by a health care provider, critical review of symptoms for possible alternative causes, and confirmation of timing of exposure to unconventional natural gas well relative to symptom onset or exacerbation. Our findings confirm earlier studies and add to the growing body of evidence of the association between symptoms and exposure to UNGD.

1. Background

The public's health should be a consideration when there is widespread adoption of new industrial activity such as extraction of natural gas through hydraulic fracturing, commonly referred to as “fracking”. Hydraulic fracturing, the injection of pressurized water, chemicals and sand into a well bore to increase production of oil or gas, was first used in conventional vertical wells drilled into discrete oil or gas reservoirs. In recent years, the development of high volume, high pressure hydraulic fracturing, combined with directional drilling, has facilitated the extraction of oil and gas from unconventional reservoirs, such as shale and other “tight” geologic formations, where the oil and gas is distributed throughout the formation rather than in defined reservoirs. Proponents of hydraulic fracturing cite benefits such as reduced dependence on foreign oil and job creation in local communities. Public health professionals and others have raised concerns about short- and long-term health and environmental impacts.

Hydraulic fracturing is part of a larger process of extracting, processing and transporting natural gas. Taken together, it is referred to as unconventional natural gas development (UNGD). UNGD sites include well pads, where the hydraulic fracturing occurs, compressor stations, metering stations, and processing plants, all of which release emissions.

Air and water monitoring near well pads have documented the presence of multiple compounds with known human health effects, both short- and long-term. Compounds of concern are volatile organic compounds including benzene, associated with short-term effects of headache and dizziness and long-term effects of aplastic anemia and leukemia (ATSDR, 2015); toluene, associated with headaches, sleepiness, confusion, and possible permanent neurological damage (ATSDR, 2011a) ethylbenzene, associated with symptoms of eye and throat irritation and a possible carcinogen (ATSDR, 2011b) and xylene, associated with eye, nose, throat, and skin irritation and possible long-term neurologic effects (CCOHS, 2017).

Other compounds with documented adverse health outcomes

* Corresponding author.
E-mail addresses: bweinberger@environmentalhealthproject.org (B. Weinberger), lgreiner@environmentalhealthproject.org (L.H. Greiner), lwalleigh@environmentalhealthproject.org (L. Walleigh), bweinberger@environmentalhealthproject.org (D. Brown).

http://dx.doi.org/10.1016/j.pmedr.2017.09.002
Received 24 March 2017; Received in revised form 11 July 2017; Accepted 1 September 2017
Available online 14 September 2017

include particulate matter, associated with asthma attacks, acute bronchitis, and reduced lung function (OSHA, 2013), methylene chloride, associated with cancer (ATSDR, 2011c), and hydrogen sulfide, associated with eye, nose, and throat irritation and asthma (ATSDR, 2011d). Our understanding of the human health impacts of exposure, however, is hampered by the absence of human toxicity information on 75–80% of the chemicals used in this process (Elliott et al., 2016). In addition to chemical emissions, UNGD produces noise and light exposures at levels that may increase the risk of adverse health outcomes, including annoyance, sleep disturbance, and cardiovascular symptoms (Hays et al., 2017).

Self-report studies have consistently documented skin irritation and rash; respiratory symptoms including difficulty breathing; nose, throat, and sinus problems; gastrointestinal disturbances; headache; sleep disruption; and psychological symptoms including stress (Saberi, 2013; Ferrar et al., 2013; Rabinowitz et al., 2015; Steinzor et al., 2013). These studies relied on self-report of symptoms, obtained either through a survey "check-list" that was self-administered (Saberi, 2013; Steinzor et al., 2013) or administered by a research assistant (Rabinowitz et al., 2015). In one study a semi-structured interview was used (Ferrar et al., 2013). With the exception of the study conducted by Rabinowitz and colleagues (Rabinowitz et al., 2015), these studies used convenience samples that ranged in size from 33 to 108. Rabinowitz et al. used randomized subject selection and did not refer explicitly to UNGD in the survey process. Two studies included an estimate of exposure. Steinzor et al. demonstrated compounds with known human health effects in air and water samples; symptoms reported by participants were consistent with these effects. Rabinowitz et al. found increased prevalence of skin and respiratory symptoms was associated with increased proximity to natural gas wells.

Limitations of the self-report studies include the use of convenience samples and possible recall bias on the part of the participant. Onset and/or exacerbation of self-reported symptoms may be subject to recall bias on the part of the participant, particularly if the participants have a high level of awareness of the risks associated with exposure and/or understand the purpose of the study. None of the self-report studies incorporated review of data by a health care provider.

More recently, several population-based studies using publicly available or health system data have documented an association with poor birth outcomes (Casey et al., 2015; McKenzie et al., 2014; Stacy et al., 2015) asthma exacerbation (Rasmussen et al., 2016), infant mortality (Busby and Mangano, 2017), and childhood acute lymphocytic leukemia.(McKenzie et al., 2017) One other study demonstrated an association with migraine, chronic rhinosinusitis, and fatigue, symptoms previously documented in the other self-report studies. (Tustin et al., 2016)

The purpose of the present study is to describe the symptoms reported in a sample of Pennsylvania residents who lived in close proximity to unconventional gas wells. We conducted a retrospective review of 135 health assessment records of individuals who live in the Marcellus Shale region of the United States. The health assessments had been conducted by family nurse practitioners in collaboration with an occupational medicine physician. Because available evidence suggests that health impacts are related to proximity to wells, with symptoms more likely in individuals who live in closer proximity to gas wells (Rabinowitz et al., 2015; Casey et al., 2015; McKenzie et al., 2014; Stacy et al., 2015; Rasmussen et al., 2016; McKenzie et al., 2017; Tustin et al., 2016), this review was restricted to the records of individuals who lived within 1 km of at least one gas well. The study was reviewed and approved by the Duquesne University Institutional Review Board.

2. Method

Family nurse practitioners at the Southwest Pennsylvania Environmental Health Project (EHP) have been systematically collecting health data from residents of communities located near UNGD sites since 2012. This service was developed to meet the needs of residents who were concerned about health impacts and who sought evaluation by a health care professional. Services are advertised on the EHP website, local media, community meetings, and word-of-mouth and are offered at no charge. The health records of these clients provide a dataset of health symptoms reported by those living in proximity to UNGD sites.

Between February 1, 2012 and October 31, 2015, 135 children and adults completed the standardized health assessment, typically conducted face-to-face by a family nurse practitioner. The health assessments were conducted according to standard clinical practice for collecting a medical history and included current problems, review of systems, past medical history, family history, and social history. When indicated by the interview, a targeted physical examination was conducted. Individuals who completed this health assessment did so for their own personal health information.

All 135 records were reviewed by a team of health care providers that included a physician who is board certified occupational medicine (LW) and at least one nurse practitioner. Records were excluded if they were incomplete at the time of the review ($n = 2$); the client was < 18 years of age ($n = 21$); the client reported employment in the gas industry ($n = 7$); client resided in a state other than Pennsylvania ($n = 28$); client did not report any symptoms at the time of the health assessment ($n = 3$). After these exclusion criteria were applied, 74 records remained.

2.1. Proximity to unconventional natural gas wells

One author (BW) used publicly available data to determine the number of unconventional natural gas wells located within 1 km of each residence for the 74 records. Publicly available data includes location and "SPUD" date, or date drilling began. Using ArcGIS, the home address was used to calculate the distance from the home to the nearest well(s). Records were excluded if it was not possible to verify at least one gas well within 1 km of the residence ($n = 23$). After this criterion was applied, 51 records remained.

2.2. Symptom inclusion criteria

Prior to review of the records, the physician (LW) and nurse practitioner developed and implemented the symptom inclusion criteria. Each symptom recorded in the health assessment was reviewed in the context of past medical and surgical history, concurrent medical conditions, family and social history, and environmental exposures unrelated to UNGD. If a plausible cause for the symptom was identified, the symptom was not included in the analysis. For example, if the social history indicated a ½ pack/day smoking history, the symptom of "difficulty breathing" was not included. Symptoms were included only when there was no possible cause evident in the health assessment record. The records were not reviewed with the intent of establishing or confirming a diagnosis, but to determine if a plausible explanation for the symptom could be identified.

Independently, BW determined timing of the exposure for each symptom that met the inclusion criteria, using the SPUD date for each unconventional natural gas well within 1 km. The earliest SPUD date for wells within 1 km of the residence was considered the beginning of exposure to UNGD. The date of onset/exacerbation of each symptom was available in the health assessment record. If the date of onset/exacerbation of a symptom occurred prior to the earliest SPUD date for wells within 1 km, that symptom was not included in the analysis. Symptoms were included only if the onset/exacerbation occurred after the date of first exposure, estimated by the earliest SPUD date.

Descriptive statistics were used to determine frequency, distribution, and variance.

Table 1
Symptoms meeting inclusion criteria that were reported between February 2012 and October 2015 by 51 adults who lived within 1 km of an unconventional natural gas well in Pennsylvania.

Symptoms	# Reporting	% Reporting
Sleep disruption	22	43.1%
Headache	21	41.2%
Throat irritation	20	39.2%
Stress/anxiety	19	37.3%
Cough	17	33.3%
Shortness of breath	15	29.4%
Sinus problems	15	29.4%
Fatigue	12	23.5%
Nausea	12	23.5%
Wheezing	11	21.6%
Itchy eyes	11	21.6%
Weak/drowsy	9	17.6%
Abdominal pain	9	17.6%
Irritable moody	9	17.6%
Painful/dry eyes	8	15.7%
Painful joints	8	15.7%
Rash	8	15.7%
Dizziness	8	15.7%
Nose bleeds	7	13.7%
Tinnitus	7	13.7%
Aches	7	13.7%
Memory - short term	7	13.7%
Numbness	7	13.7%
Chest pain	6	11.8%
Hair loss	6	11.8%
Itchy skin	6	11.8%
Worry	6	11.8%
Palpitation	5	9.8%
Skin lesions/blisters	5	9.8%

3. Results

The 51 adults included in this record review had reported at least one symptom on their health assessment, denied occupation exposure related to natural gas extraction and lived in Pennsylvania within 1 km of an unconventional natural gas well. The average age of this sample was 57 (SD = 12.3), with a range of 24–85. More than half (56.8%) were female and the majority (83%) were married. Each individual lived within 1 km of a gas well; the number of wells ranged from 1 to 16, (mean 5.7, SD 3.6). A total of three counties in Pennsylvania are represented in this sample: Washington (n = 47), Butler (n = 3), and Bedford (n = 1) counties.

In this sample, all individuals reported at least one symptom at the time of the health assessment. The number of symptoms reported ranged from 1 to 19, with an average of 7.2 (SD = 4.9). Not all of the symptoms reported met the inclusion criteria (i.e., symptoms began or worsened after exposure to UNGD and could not be explained by a pre-existing or concurrent health condition). Some symptoms reported by 19 individuals (37%) did not meet inclusion criteria and were excluded, although the individuals remained in the analysis. The number of symptoms excluded/individual ranged from 1 to 7, with an average of 2.4 symptoms. For five of the 19 individuals, all reported symptoms were excluded.

The number of symptoms meeting inclusion criteria ranged from 0 to 19 with a mean of 6.2 (SD = 5.1) symptoms/individual. The most frequently reported symptoms that met inclusion criteria were sleep disturbance, headache, throat irritation, stress/anxiety, cough, shortness of breath, sinus, fatigue, wheezing, nausea (> 20% of sample).

Symptoms shown in Table 1 were reported by at least 10% of the sample. Symptoms not shown on Table 1, reported by < 10% of the sample were: weight change, hearing loss, vomiting, burning skin, and depression.

4. Discussion

The symptoms reported by residents of southwestern Pennsylvania who live within 1 km of an unconventional natural gas well are consistent with those reported in other self-report studies. The most commonly reported symptoms in this sample of adults were sleep disruption, headache, throat irritation, stress/anxiety, cough, shortness of breath, sinus problems, fatigue, nausea, and wheezing.

Limitations of this study include use of self-report data and a convenience sample. However, our methodology mitigates some of the limitations typically associated with this type of data and strengthens our results. Reported symptoms were abstracted from health records obtained by a nurse practitioner in consultation with a physician. Each symptom was evaluated using criteria to establish onset or exacerbation of the symptom relative to exposure to UNGD and to rule out other plausible explanations for the symptom. Only those symptoms that could not be explained by evidence in the health record (i.e., medical, surgical, or social history) and had a date of onset or exacerbation after exposure to UNGD began were included in the analysis.

Both the collection of symptom data, and the inclusion criteria used, distinguish this study from others that rely only on self-report. In comparison to such studies, our results are strengthened by the collection of health assessment data by a health care provider, critical review of symptoms for possible alternative causes, and confirmation of timing of exposure relative to symptom onset or exacerbation.

Health care providers whose clients live or work in communities where unconventional techniques are used to extract natural gas and/or oil should be alert to the possibility of environmental exposures. Symptoms, particularly those that are unexplained by concurrent medical conditions, may be related to environmental exposures.

Funding

This work was supported by Heinz Endowments (E4442), Pittsburgh, PA. Heinz Endowments had no role in study design; collection, analysis and interpretation of data; writing of the report; or the decision to submit the article for publication.

Conflict of interest

The authors declare no conflict of interest.

References

ATSDR, 2011a. Toluene. Available at: Agency for Toxic Substances and Disease Registry Toxic Substances Portalhttp://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=29, Accessed date: 13 February 2017.

ATSDR, 2011b. Ethylbenzene. Available at: Agency for Toxic Substances and Disease Registry Toxic Substances Portalhttps://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=66, Accessed date: 13 February 2017.

ATSDR, 2011c. Methylene chloride. Available at: Agency for Toxic Substances and Disease Registry Toxic Substances Portalhttp://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=42, Accessed date: 13 February 2017.

ATSDR, 2011d. Hydrogen sulfide carbonyl sulfide. Available at: Agency for Toxic Substances and Disease Registry Toxic Substances Portalhttp://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=67, Accessed date: 13 February 2017.

ATSDR, 2015. ToxFAQsTM for benzene. Available at: Agency for Toxic Substances and Disease Registry Toxic Substances Portalhttps://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=38&tid=14, Accessed date: 13 February 2017.

Busby, C., Mangano, J., 2017. There's a world going on underground—infant mortality and fracking in Pennsylvania. J. Environ. Prot. 8, 381–393.

Casey, J.A., et al., 2015. Unconventional natural gas development and birth outcomes in Pennsylvania, USA. Epidimiology. http://dx.doi.org/10.1097/EDE.0000000000000387.

CCOHS, 2017. Xylene. Available at: Canadian Centre for Occupational Health and Safety OSH Answers Fact Sheethttp://www.ccohs.ca/oshanswers/chemicals/chem_profiles/xylene.html, Accessed date: 13 February 2017.

Elliott, E.G., Ettinger, A.S., Leaderer, B.P., Bracken, M.B., Deziel, N.C., 2016. A systematic evaluation of chemicals in hydraulic-fracturing fluids and wastewater for reproductive and developmental toxicity. J. Expo. Sci. Environ. Epidemiol. http://dx.doi.org/10.1038/jes.2015.81.

Ferrar, K.J., et al., 2013. Assessment and longitudinal analysis of health impacts and

stressors perceived to result from unconventional shale gas development in the Marcellus Shale region. Int. J. Occup. Environ. Health 19, 104–112.
Hays, J., McCawley, M., Shonkoff, S.B.C., 2017. Public health implications of environmental noise associated with unconventional oil and gas development. Sci. Total Environ. 580, 448–456.
McKenzie, L.M., et al., 2014. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ. Health Perspect. 122, 412–417.
McKenzie, L.M., et al., 2017. Childhood hematologic cancer and residential proximity to oil and gas development. PLoS One 12, e0170423.
OSHA, 2013. Diesel exhaust. Available at: Occupational Health and Safety Administration Safety and Health Topicshttps://www.osha.gov/SLTC/dieselexhaust/.
Rabinowitz, P.M., et al., 2015. Proximity to natural gas wells and reported health status: results of a household survey in Washington County, Pennsylvania. Environ. Health Perspect. 123, 21–26.
Rasmussen, S.G., et al., 2016. Association between unconventional natural gas development in the Marcellus Shale and asthma exacerbations. JAMA Intern. Med. http://dx.doi.org/10.1001/jamainternmed.2016.2436.
Saberi, P., 2013. Navigating medical issues in shale territory. New Solut. J. Environ. Occup. Health Policy 23, 209–221.
Stacy, S.L., et al., 2015. Perinatal outcomes and unconventional natural gas operations in Southwest Pennsylvania. PLoS One 10, e0126425.
Steinzor, N., Subra, W., Sumi, L., 2013. Investigating links between shale gas development and health impacts through a community survey project in Pennsylvania. New Solut. J. Environ. Occup. Health Policy 23, 55–83.
Tustin, A.W., et al., 2016. Associations between unconventional natural gas development and nasal and sinus, migraine headache, and fatigue symptoms in Pennsylvania. Environ. Health Perspect. http://dx.doi.org/10.1289/EHP281.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

FROM THE AMERICAN ACADEMY OF PEDIATRICS

TECHNICAL REPORT

Insufficient Sleep in Adolescents and Young Adults: An Update on Causes and Consequences

Judith Owens, MD, MPH, FAAP, ADOLESCENT SLEEP WORKING GROUP, and COMMITTEE ON ADOLESCENCE

KEY WORDS
adolescents, caffeine, car crashes, media use, obesity, sleep loss, sleepiness

ABBREVIATIONS
REM—rapid eye movement

www.pediatrics.org/cgi/doi/10.1542/peds.2014-1696

doi:10.1542/peds.2014-1696

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

abstract

FREE

Chronic sleep loss and associated sleepiness and daytime impairments in adolescence are a serious threat to the academic success, health, and safety of our nation's youth and an important public health issue. Understanding the extent and potential short- and long-term repercussions of sleep restriction, as well as the unhealthy sleep practices and environmental factors that contribute to sleep loss in adolescents, is key in setting public policies to mitigate these effects and in counseling patients and families in the clinical setting. This report reviews the current literature on sleep patterns in adolescents, factors contributing to chronic sleep loss (ie, electronic media use, caffeine consumption), and health-related consequences, such as depression, increased obesity risk, and higher rates of drowsy driving accidents. The report also discusses the potential role of later school start times as a means of reducing adolescent sleepiness. *Pediatrics* 2014;134:e921–e932

INTRODUCTION

Since the publication of the American Academy of Pediatrics technical report on excessive sleepiness in adolescents in 2005,[1] there have been a considerable number of articles published pertaining to sleep. These articles expand on many of the topics raised in the original report and add a number of new important health issues not previously or minimally discussed (ie, short sleep and its association with obesity, caffeine/stimulant use). The previous technical report provided an overview of the profound changes in sleep–wake regulation and circadian biology occurring during adolescence, outlined factors (ie, parental influence, school start times) contributing to insufficient sleep in adolescents, and summarized consequences such as negative impacts on mood, attention, and school performance. It also focused in particular on clinical sleep disorders such as insomnia, narcolepsy, and restless legs syndrome contributing to daytime sleepiness in adolescents. The new material in the present report adds to what is known about the extent of sleep restriction in the adolescent population and reinforces the importance of recognizing insufficient sleep both as a key public health issue and one that is immediately relevant to pediatric practice.

The focus of this updated technical report is on insufficient sleep, specifically as a consequence of voluntary sleep restriction. It should

be noted that such terms as insufficient sleep, inadequate sleep, short sleep duration, sleep loss, and sleep restriction are used interchangeably and as generic descriptive terms only and do not imply specific amounts but rather "less sleep than needed."

Insufficient sleep in adolescents was recognized as a serious health risk in 2010 in a jointly sponsored American Medical Association/American Academy of Sleep Medicine resolution acknowledging the problem.[2] Furthermore, objectives for Sleep Health, a new topic in Healthy People 2020,[3] specifically includes reducing adolescent sleep loss: "SH-3: Increase the proportion of students in grades 9 through 12 who get sufficient sleep" (defined as ≥8 hours).

A second focus of the present report is on unhealthy sleep behaviors (ie, poor "sleep hygiene") in teenagers, including irregular sleep–wake patterns, electronic media use in the bedroom, and excessive caffeine use. A third focus is on the myriad of potential consequences of inadequate sleep in adolescents, including depression/suicidal ideation, obesity, car crashes attributable to drowsiness, and poor academic performance.

EPIDEMIOLOGIC STUDIES OF SLEEPING ADOLESCENTS

Epidemiologic studies of sleep typically rely on self- or parent-reported questionnaire data to document adolescent sleep patterns and the factors affecting them. The key advantage of this method is the ease of assessment of large sample sizes. As a result, epidemiologic studies can determine sleep patterns across the full adolescent age range with less potential sampling bias than smaller case-control studies. Consistent with other methodologic approaches, the consensus finding across epidemiologic studies is that both younger[4–6] and older[4,7–11] adolescents are not getting enough sleep. It is important to note that studies comparing self-reported sleep duration with objectively measured sleep amounts (ie, with actigraphy) suggest that self-reports of sleep often overestimate actual sleep duration, signifying that the problem of chronic sleep loss in adolescents may be even greater than the data indicate.[12]

US-based[4,13] and international studies[5,6,14] revealed that as students get older, sleep durations decline. The National Sleep Foundation Sleep in America Poll[4] found that by the 12th grade, 75% of students self-reported sleep durations of less than 8 hours of sleep per night compared with 16% of sixth graders. Furthermore, although 30% to 41% of sixth through eighth graders were getting 9 or more hours of sleep, only 3% of 12th graders reported doing so. Adolescents often attempt to address the accumulated weekday sleep debt during the weekend, when oversleep (the difference between weekday and weekend sleep durations) of up to 2 or more hours is commonly reported.[4,7,8,15,16]

Comparisons with other countries show similar patterns of decreased sleep durations with increasing age among adolescents. For example, in Northern Taiwan,[5] Germany,[14] and India,[17] average sleep duration dropped to below 8 hours for high school–aged students. The most precipitous drop was reported in 2005 for more than 1400 South Korean adolescents, for whom the average duration of sleep was 4.9 hours.[6] In general, studies have demonstrated similar weekend sleep durations across countries, but weekday sleep durations tend to vary greatly.[5,9] In contrast, Australian adolescents seem to do comparatively well, with students 17 years and older reporting average sleep durations between 8.5 and 9.1 hours.[18] The difference between weeknight and weekend sleep durations also was not large, with weekend durations reported at 9.3 hours. Interestingly, although data on school start times in the Australian study were not presented, the average reported wake times on school days was 7:00 AM or later, suggesting that the schools these students attended did not start before 8:00 AM.

A number of studies have indicated that sleep health disparities exist and that adults,[19] children, and adolescents[20–22] from families with low income or of racial or ethnic minorities may be at even greater risk of poor-quality and insufficient sleep. For example, in a recent study of middle school students, appropriate timing and consistency of both weeknight and weekend sleep schedules were inversely correlated with low socioeconomic status and specific household/neighborhood variables (eg, overcrowding, noise levels, safety concerns).[23] This relationship may have important health implications. For example, a recent study suggested that less sleep was a predictor of obesity risk in African-American adolescents but not in white adolescents.[24] "Missed" sleep was also reported to be an important factor in asthma morbidity, especially in Latino children.[25] However, higher socioeconomic status is not necessarily protective because studies have also shown that youth from households with higher socioeconomic status have shorter sleep durations.[16,26]

For older adolescents, additional environmental factors, such as after-school employment,[16] striving for good grades,[5,6,12] socializing,[27,28] participation in sports and other extracurricular activities, and lack of parental monitoring or rules about bedtimes, can further interfere with sleep durations.[6,29,30] School start times are reviewed later in the present report.

In summary, short sleep durations, coupled with evidence of daytime sleepiness (eg, increased self-reported sleepiness ratings,[5,6,11,31] daytime napping,[5,14,26] weekend oversleeping,[6,10,14,32] need for assistance in waking[6]), as well as increased use of fatigue countermeasures

(eg, excessive caffeine consumption[4,5,15]), all indicate that adolescents are sleeping fewer hours than they need. The clear and consistent message is that middle and high school students are not getting enough sleep and that this issue is a chronic problem worldwide. In addition, the health and behavioral outcomes linked to restricted sleep, as further detailed in the following sections, are alarming. These outcomes include increased risk of car crashes,[4,33] delinquent behaviors,[27] depression,[8,10,34] and psychological stress.[35]

FACTORS CONTRIBUTING TO INSUFFICIENT SLEEP IN ADOLESCENTS

Influence of Biological Processes on Adolescent Sleep

The association of early adolescent development/pubertal onset and a more evening-type circadian phase preference (ie, preferred timing of sleep and wake as well as daytime activities) has been documented since the 1990s.[36] The behavioral result of this biological process is most clear in the timing of sleep, particularly for weekends. For example, Roenneberg et al[37] measured the midpoint of weekend sleep in European schoolchildren and revealed a marked linear delay of 2 (girls) to 3 (boys) hours across the second decade, roughly 12 to 18 minutes later with each year of age. The reversal of this delayed weekend sleep pattern may be a "biological marker for the end of adolescence."

Recent data have indicated that another process involved in regulating sleep timing seems to be altered to favor late nights across adolescent development. This process, called sleep–wake homeostasis, can be thought of as the system that accounts for greater pressure to sleep as one stays awake longer. Data collected with 2 different paradigms to estimate the rate of buildup of sleep pressure in prepubertal versus postpubertal adolescents indicate that more mature adolescents accumulate this sleep pressure at a slower rate.[38,39]

Maturational changes to these 2 bioregulatory processes begin in adolescents as young as middle school and present a major challenge for young people to fall asleep in the early evening and to wake refreshed/restored in the early morning to attend school. The most prominent factors in this regard are evening and nighttime screen use and social networking, both of which have increased markedly in the 21st century.[40] Going to bed later and waking later on weekends than on weekdays reflects the biology of circadian rhythm and is also a response to insufficient weekday sleep. Later sleep timing and catch-up sleep on the weekends further delay the signal for the biological night (ie, melatonin production) and dissipate residual sleep pressure.[41] In summary, the combination of biologically driven processes with modern lifestyles and social obligations minimize the opportunities for adolescents to obtain adequate sleep.

Electronic Media and Sleep

Today's adolescents and young adults have grown up in an electronic age. According to the National Sleep Foundation's 2006 Sleep in America Poll, almost all adolescents had at least 1 media electronic device in their bedroom.[4] Among the devices reported were televisions (57%), music players (90%), video game consoles (43%), computers (28%), and phones (64%). A more rigorous study of subjects recruited from a pediatric office in a Philadelphia suburb showed that of the 100 adolescents ranging in age from 12 to 18 years, two-thirds had a television in their bedroom, almost one-third had a computer, almost 80% had a digital music player, and 90% had a cellular phone in their bedroom.[42] The teenagers engaged simultaneously in an average of 4 electronic activities after 9:00 PM.

It is not surprising that several studies in adolescents have demonstrated that electronic exposure in the evening potentially disrupts sleep. The use of multiple electronic devices at the same time has been associated with less sleep at night and a greater degree of sleepiness during the daytime.[4,15,31,42,43] Having a television in the bedroom (or even out of the bedroom) has been associated with later bedtimes on weekdays, longer sleep latencies, shorter total sleep times, later wakeup times on the weekends, and more daytime sleepiness in adolescents.[44–46] In the Children in the Community Study in 1976,[47] adolescents who were watching 3 or more hours of television not only experienced difficulty falling asleep and frequent awakenings but also had a risk of having difficulties with their sleep later in adolescence and young adulthood. The use of computers before bedtime has also been shown to have the same effect, and this finding has been demonstrated in a wide range of countries and cultures.[45,46,48–51]

Engaging in a greater number and range of sleep-interfering activities before going to bed has also been associated with less nocturnal sleep and more daytime sleepiness in adolescents.[45] Several mechanisms have been postulated about how media disrupts sleep.[40] One is that the use of media directly displaces sleep; an adolescent or young adult may simply stay up later enjoying whatever media he or she is using. In addition, electronic media allow for greater interaction between friends. Early data suggested that peer-to-peer interaction did not have a major influence on school-night bedtime but rather had a more significant influence on a teenager's sleep on weekends.[52] These findings may no

longer hold now that there are enhanced ways for adolescents to communicate electronically. Calamaro et al[42] found that after 9:00 PM, 34% of adolescents in the study sample were text messaging, 44% were talking on the phone, 55% were online, and 24% were playing computer games. In another study of Belgian teenagers, 62% of the subjects used their phones after the lights were turned off, and phone use at this time was associated with increased daytime tiredness the next day.[53]

Another possible mechanism for the detrimental effect of electronics use on sleep is that the light produced by electronic devices may disrupt circadian rhythms by suppressing melatonin, resulting in the inability to fall asleep at a reasonable time.[40] Recent studies have demonstrated that exposure to relatively low-intensity light can alter circadian rhythms[54,55] and suppress nocturnal melatonin secretion.[56]

Finally, media use may cause increased sleep-disrupting mental, emotional, and physiologic arousal.[40] One study found that subjective sleepiness was lower, sleep latency was longer, and rapid eye movement (REM) sleep was shorter in subjects after playing video shooting games, independent of the brightness of the screen used.[56] Another study that compared playing an interactive computer game with watching a movie on television in the evening[51] found a decline in verbal memory performance, prolonged sleep latency, and an increase in light sleep in the computer game cohort.

School Start Times

As has been described elsewhere in the present report, a multitude of changes occur over the course of adolescence that can affect the quality and quantity of sleep in adolescents and young adults. One of the most salient and arguably most malleable is that of school start times, a systemic countermeasure. There are clearly a number of practical implications and/or challenges that schools might face when considering altering school start times, such as changes in athletic schedules, effects on after-school activities, and transportation issues.[57] Despite these hurdles, a small yet increasing number of school districts over the last 15 years have responded to research reports regarding the prevalence of inadequate sleep among middle and high school students by delaying school start times. Research on the effects of delaying the start times of middle and high schools for adolescents' sleep and daytime functioning is discussed in this section, and a more detailed discussion is available in the American Academy of Pediatrics policy statement on school start times.[58]

In one of the first studies to assess the effect of school start times on adolescents,[59] a 65-minute earlier school start time in the transition from grade 9 to grade 10 resulted in fewer than one-half of 10th graders obtaining an average of 7 hours or more of sleep on school nights and physiologic levels of daytime sleepiness ordinarily seen in patients with narcolepsy. A large prospective longitudinal study of delays in school start times in both an urban and a suburban school district found improvements in attendance rates and an increase in the percentage of high school students continuously enrolled in the district or the same school, although grades did not show a statistically significant improvement.[60] Similar to what has been reported in subsequent studies,[55] bedtimes did not change with the delay in start times, but morning wake times were significantly later, resulting in the students obtaining nearly 1 hour more of sleep on school nights. Other studies have also reported increases in sleep duration and decreased daytime sleepiness associated with delayed school start times,[61] as well as increased satisfaction with sleep and motivation and significant declines in self-reported depressed mood, health center visits for fatigue-related complaints, and first-period tardiness.[62]

Research on the effects of early versus delayed school start times for young adolescents has resulted in strikingly similar findings. Students at later-starting middle schools report later rise times, more total sleep on school nights, less daytime sleepiness, less tardiness, fewer attention/concentration difficulties, and better academic performance compared with middle school students at earlier-starting schools.[63,64] In addition, middle school students with a delayed start time of 1 hour for just 1 week performed better than the earlier-starting comparison group on tests requiring attention.[65] Undoubtedly, delaying the start of middle school allows early adolescents, similar to their older high school–aged peers, to obtain sufficient sleep and to perform better in school.

Danner and Phillips[33] demonstrated that delaying school start times in 1 community in Kentucky decreased the average crash rate for teenaged drivers by 16.5%, while the state as a whole increased by 7.8% in the same time period. In another recent study conducted in 2 adjacent, demographically similar cities, there were significantly increased teenaged (16- to 18-year-olds) crash rates over a 2-year period in the city with earlier high school start times.[66]

Taken together, it is clear that when middle and high schools (schools designed for adolescents) institute the countermeasure of delaying the start time of school, students obtain more sleep and there are associated improvements in behaviors pertinent to academic success (attendance and school performance) and safety.

Caffeine

Use of caffeine has been understudied in adolescents and children; however, current research has raised important questions regarding the complex interrelationship between caffeine use and sleep patterns during this developmental period.[67–70]

Similar to studies of adult caffeine use, higher caffeine intake as early as 12 years of age is associated with shorter sleep duration, increased sleep onset latency, increased wake time after sleep onset, and increased daytime sleepiness.[68,69,71] High school students who report a moderate to high intake of caffeine versus very low intake were nearly 2 times more likely to have difficulty sleeping and to report morning sleepiness.[71] High and regular caffeine users seem to develop a cycle in which disrupted sleep attributable to caffeine use leads to sleepiness, which then leads them to increase their caffeine consumption.[72] Moreover, caffeine reduces the percentage of time spent in slow-wave or "deep" sleep in a dose-related manner and alters the temporal organization of REM/non-REM sleep.[70,72,73] This outcome is particularly important because of the critical role that both slow-wave sleep and REM sleep play in learning and memory consolidation.

Researchers are beginning to examine adolescents' expectancies regarding caffeine use. Reported expectancies for caffeine users were for energy and mood enhancement and to counteract the effects of sleep disturbances. Other studies have found that adolescents report using energy drinks for the energy boost or "buzz" and that these beverages make them "feel more energetic."[74] In comparing different types of users, "mixed" caffeine product users (ie, soda, coffee, energy drinks) reported higher levels of withdrawal and/or dependence, energy and mood enhancement, appetite suppression, and performance enhancement expectancies than either the high-soda or low-caffeine use groups. A higher percentage of mixed users compared with high-soda users reported that the reasons for their caffeine use were related to getting through the day, experimentation, and recreation.[68]

Regardless of the reasons adolescents use caffeinated substances, there are clear consequences. Adolescents experience tolerance and withdrawal symptoms; however, in general, caffeine dependence in adolescents is poorly understood.[75,76] Female high school students were more likely to report withdrawal/dependence caffeine expectancies as well as appetite suppression expectancies compared with their male peers.[68] Although adolescents may consume excessive caffeine in an attempt to mitigate daytime sleepiness, this action not only further compromises the quality and quantity of sleep, but high caffeine users may also be at risk for other substance use and/or abuse as well as other risk-taking behaviors.[68,75,77–79] Consumption of caffeine is linked to nicotine use in adolescents,[80] which in turn may further disrupt sleep[81] and perpetuate the cycle of sleep fragmentation/daytime sleepiness coupled with stimulant use. Not surprisingly, increased caffeine use frequently coexists with other behaviors that negatively affect sleep, such as adolescents' late-night, multifaceted technology use. For example, a recent study[42] found that high school–aged adolescents who reported the highest levels of multitasking with media-related electronic products also consumed the most caffeine.

The correlation between caffeine consumption and daytime sleepiness is, in turn, inversely correlated with academic achievement. For example, 1 study of over 7000 adolescents reported that a significant proportion of the variance that occurs in academic achievement was found to be attributable to caffeine use.[82] The authors further postulated that daytime sleepiness might be an important mediator of the negative impact of not only caffeine but also alcohol use and cigarette smoking on academic success. Caffeine use may also serve as an affect modulator, particularly when it comes to adolescents with excessive daytime sleepiness or insufficient sleep. For example, studies have suggested that adolescents may use caffeine as a means of regulating mood and/or helping to alleviate depression.[75,83]

Undoubtedly, there is growing evidence that caffeine use is increasing among adolescents, with negative implications for sleep and other behaviors. Significant questions, however, remain regarding the direction of this complex relationship. Are adolescents turning to caffeine because of insufficient and inconsistent sleep patterns, or does increased caffeine use exacerbate sleep problems for developing adolescents? These findings document the need for more extensive health education about caffeine use during adolescence. Furthermore, with the dramatic and potentially dangerous rise in the consumption of energy drinks in combination with alcohol (particularly on college campuses), researchers and physicians need to carefully investigate the implications for adolescents across the developmental spectrum.[84]

Other Factors Affecting Sleep in Adolescents

A number of other factors have been related to reduced sleep durations across the adolescent age range, such as chronic medical illnesses, mental health issues (ie, anxiety/stress), and prescribed psychotropic medications.[10,15] Chronic respiratory illnesses, such as asthma, and pain conditions, such as migraines, may contribute to truncated and disrupted sleep. Although obesity

does not necessarily lead to poor sleep per se, it is an increasingly important risk factor for obstructive sleep apnea in adolescents, which in turn results in poor-quality sleep and daytime consequences. Moreover, although the evidence is still largely anecdotal, the use of stimulants (particularly those typically prescribed for the treatment of attention-deficit/hyperactivity disorder) as a "countermeasure" to sleepiness and/or as academic "performance enhancers" seems to be an increasingly common phenomenon across college campuses.[85,86] Future investigations need to assess the extent and context of "diversion" of legitimately prescribed stimulant medications as well as the use and abuse of increasingly diverse alternative sources of caffeine (eg, caffeinated alcoholic beverages, candy, foodstuffs). Finally, it should also be noted that both over-the-counter (ie, diphenhydramine) and prescription (ie, zolpidem) medications taken by adolescents to induce sleep may result in residual daytime sleepiness and that commonly used medications (eg, decongestants) and prescription drugs (eg, activating antidepressants [eg, fluoxetine], stimulant medication for attention-deficit/hyperactivity disorder) may also result in disrupted sleep and consequent daytime sleepiness in adolescents.

CONSEQUENCES OF INSUFFICIENT SLEEP

It is important to recognize that the causes and consequences of chronic sleep loss in adolescents are often closely intertwined in complex ways, further exacerbating the situation. For example, alcohol consumption can lead to insufficient and poor-quality sleep and subsequent daytime sleepiness.[10,32,87] In turn, chronic sleep loss has been linked to an increased risk of alcohol and drug use.[14,28,34] Similarly, compensatory oversleep behavior on weekends provides some temporary relief from sleepiness generated by insufficient sleep on weekdays, but it also leads to disrupted sleep–wake cycles, exacerbation of the normal adolescent circadian phase delay, and perpetuation of compromised weekday alertness. Moreover, consequences such as poor judgment, lack of motivation, and inattention and affective dysregulation resulting from sleep loss, as well as the effect of insufficient sleep on decision-making skills,[88] further compound the potential negative effects in adolescents. In particular, higher level cognitive "executive functions," for which adolescence is a critical period of evolution, are selectively affected by sleep loss.[89]

Sleep Loss and Depression, Mood Disturbances, and Suicidal Ideation

It has long been recognized that mood disorders (especially major depressive disorder) in clinical samples of adults exhibit a bidirectional relationship with sleep disturbances, and the presence of sleep problems has been shown to both increase the relative risk of developing depression[90] and to be a predictor of relapse.[91,92] Similar findings have emerged in the child and adolescent population, particularly with regard to an association between insomnia (difficulty initiating and/or maintaining sleep) and clinically diagnosed depression.[93] Recent studies have shown that addressing insomnia will greatly improve treatment of depression. Although studies examining sleep architecture in depressed adolescents[94] have not consistently replicated differences in polysomnographic findings in depressed adults (ie, increased REM sleep, decreased REM onset latency), there may be other sleep electroencephalographic markers, such as sleep spindle activity and cyclic alternating patterns,[95] that have more relevance for the adolescent population.

Sleep debt in college students has been shown to be associated with a higher risk of reporting depressive symptoms.[96] Similarly, in high school students, shorter school-night total sleep time has been associated with both daytime sleepiness and depressive symptoms,[97] whereas increased risk-taking behaviors were associated with irregular sleep patterns and self-reported sleep problems rather than sleep loss. These outcomes are similar to the findings of a large longitudinal adolescent health study in which symptoms of possible insomnia (ie, trouble sleeping, morning tiredness) predicted risk behaviors (eg, drinking and driving, smoking, delinquency) after controlling for depression symptoms.[97,98]

There is evidence that other sleep-related parameters may also have a significant effect on mood; for example, adolescent self-reported sleep variables (including trouble sleeping, tiredness, nightmares, and being a long sleeper) have been found to be significantly associated with psychological symptoms, including anxiety/depression, and withdrawal.[99] Circadian factors may also play a role in mood regulation; increased self-reported "eveningness," a marker of circadian phase delay, has also been associated with depression and lower behavior activation/positive affect.[100]

A number of recent studies have focused on the possible relationship between sleep and suicidal ideation.[101,102] Sleeping less than 8 hours at night seems to be associated with an almost threefold increased risk of suicide attempts after controlling for a number of confounding variables.[101] Not only do adolescents with insufficient sleep have an increased risk of suicidal ideation, but the risk may be similarly increased in adolescents whose parents also have insufficient sleep, raising some interesting questions about multigenerational environmental and/or genetic factors.[103] A

similar relationship has been found in middle and high school students; adolescents with parental-set bedtimes of midnight or later are significantly more likely to suffer from depression and to have suicidal ideation compared with adolescents with parental-set bedtimes of 10:00 PM or earlier. Earlier parental-set bedtimes, therefore, could potentially be protective against adolescent depression and suicidal ideation. Finally, both decreased (≤5 hours) or increased (≥10 hours) total sleep times may put adolescents at a significantly higher risk of suicidality compared with a total sleep time of 8 hours.[104] However, increased risk of the most severe forms of suicidality (attempt requiring treatment) seems to be associated with significantly shorter sleep duration (total sleep time ≤4 hours).

In summary, sleep has an important influence on mood and the development of depressive symptoms in adolescents. Although insufficient sleep and daytime sleepiness seem to have the most robust relationship with mood dysregulation, poor-quality sleep and irregular sleep patterns are also associated with depressed mood. Importantly, from a clinical standpoint, improvements in sleep may lead to improvements in mental health functioning (and vice versa). The association between sleep loss and increased suicidality in adolescents is particularly troubling and is clearly important for pediatricians to recognize.

Insufficient Sleep and Obesity Risk

A considerable body of evidence now links short sleep duration in both adults and children with an increased risk of obesity, an association that obviously has long-range health implications. With regard to mechanisms, experimental studies of sleep restriction in healthy adult volunteers have shown that there are alterations in metabolic profiles (eg, insulin, ghrelin, leptin, cortisol) associated with sleep loss, which result in insulin resistance, increased sympathetic nervous system activity, and increased hunger and decreased satiety.[105] As a result, sleep-restricted subjects consume more calories, exercise less, and consume a higher percentage of calories from fat.[106–109]

In 1 earlier study, it was estimated that for each hour sleep lost, the odds of being obese increased in adolescents by 80%.[110] Furthermore, there is evidence of a "dose–response" inverse relationship between sleep and weight,[111] with odds ratios of overweight increasing with decreasing sleep duration (<5 hours, 5–6 hours, 6–7 hours, and 7–8 hours compared with students sleeping >8 hours). The increased risk of obesity associated with insufficient sleep seems to be equivalent to or higher than the risk associated with other factors strongly correlated with weight, such as parental obesity and television viewing.[112]

Early sleep patterns may influence BMI in adolescents and young adults as well. Longitudinal data suggest that children who sleep less, have later bedtimes, or get up earlier subsequently have higher BMIs and are more likely to be overweight, even after controlling for baseline BMI.[113] This association may be established early in life; for example, an increased BMI and high prevalence of obesity in young adults was found in individuals whose mothers had reported sleeping problems ("irregular" or "troubled" sleeping) at ages 2 to 4 years (although sleep duration was not specified) compared with those who had not had sleeping problems.[114]

Although the underlying potential mechanisms for the relationship between sleep and weight in adolescents have yet to be elucidated, metabolic alterations associated with sleep loss similar to those observed in adults are likely to play an important role. In particular, perturbations in the levels of neurohormones known to be associated with hunger and satiety (eg, adiponectin, ghrelin) as well as increased insulin resistance (as measured by the homeostatic model assessment [HOMA]) have been demonstrated in adolescents sleeping <5 hours per day.[115] These "short sleepers" were also found to have a higher percentage of carbohydrate intake according to a dietary questionnaire.[116] Similarly, older adolescents sleeping less than 8 hours have been shown to consume a higher proportion of calories from fats, and shorter sleep duration is also associated with increased odds of consuming a higher percentage of daily caloric intake from snacks.[117] Importantly, these metabolic perturbations also increase the risk of development of type 2 diabetes in these obese adolescents.[118,119] Finally, it should be noted that the relationship between short sleep duration and obesity may be further complicated by the presence of obstructive sleep apnea. Not only is obesity emerging as an increasingly important risk factor for sleep-disordered breathing in children,[120] but obstructive sleep apnea may further exacerbate the inflammatory and metabolic consequences of both obesity and chronic sleep loss.[7,121–123] Some evidence also suggests there may be gender differences in the strength of the association between obesity and sleep duration, with adolescent boys seeming to be at higher risk compared with girls in both cross-sectional and longitudinal studies using large data sets.[124] However, not all studies have identified gender differences; in 1 study of junior high school students, short sleep duration was significantly associated with overweight in girls only.[125]

Finally, it should be noted that not all studies have found an inverse

relationship between sleep duration and obesity in adolescents.[126] It has been postulated that some of these discrepancies may be attributable to measurement issues; in a nationally representative sample of adolescents that included 2 different measures of sleep duration (24-hour time diaries and self-reported "usual" sleep hours), self-reported sleep duration and time-diary sleep were only weakly correlated with each other, and only self-reported sleep hours were inversely associated with overweight.[127]

In summary, despite a number of methodologic limitations, the body of evidence from studies assessing the relationship between short sleep and increased overweight/obesity risk in adolescents is both compelling and potentially far-reaching in its public health implications. More research is urgently needed to identify specific metabolic, inflammatory, and hormonal mechanisms as well as the interactions among sleepiness and activity levels, mood, cognition, and behavioral responses in this complex equation. Moving forward, both community-based obesity prevention programs, such as "Let's Move" (http://www.letsmove.gov), and clinical treatment programs for overweight and obese teenagers should include consideration of sleep as an important variable in the relative success or failure of these interventions.

Drowsy Driving in Adolescents

It is now well recognized that daytime sleepiness and fatigue are associated with an increased rate of motor vehicle crashes.[128–131] The fact that sleepiness could be a major factor in individuals without known sleep disorders was not universally accepted until the landmark paper[132] by Pack et al in 1995. This group reviewed crash reports from the state of North Carolina between 1990 and 1992 in which the driver was judged to have fallen asleep behind the wheel. In the 85% of crashes in which intoxication was not thought to be a contributing factor, the majority (55%) occurred in individuals 25 years or younger. Crashes in this younger age range generally occur at night, unlike crashes with older adults, which typically occur during the mid-afternoon,[133,134] and tend to occur predominantly when the drowsy driver is alone.[135–137] In addition, young male drivers are more likely to be involved in sleep-related crashes than are young female drivers.[132,134,136]

Sleepiness while driving is a common complaint among adolescents[136] and college students.[137] In a study of high school students with driver's licenses, one-fifth reported poor-quality sleep, almost two-thirds complained of daytime sleepiness, 40% reported having sleepiness while driving, and 11% reported having had an automobile crash in which sleepiness was the main cause. Being sleepy behind the wheel and poor-quality sleep at night also seem to increase the risk of having an automobile crash in college students.

Countermeasures may potentially help prevent traffic accidents in this age range. Avoidance of driving when sleep deprived and not drinking alcohol before getting behind the wheel are obvious solutions. Other countermeasures that have some empiric support in adults and may be effective in adolescents include planned napping.[138,139]

CONCLUSIONS

Adolescent sleep loss poses a serious risk to the physical and emotional health, academic success, and safety of our nation's youth. The prevalence and effects of insufficient sleep may be further magnified in high-risk adolescents. Pediatricians have the opportunity to make significant inroads into addressing the health risk that sleep loss presents through screening and health education efforts. Many of the factors that have been shown to contribute significantly to the current "epidemic" of insufficient sleep in teenagers, such as electronic media use, caffeine consumption, and early school start times, are potentially modifiable and, as such, are important intervention points in anticipatory guidance in the clinical setting. On the local and national levels, pediatricians need to advocate for educational, administrative, and health policies that promote healthy sleep and reduce the risk factors for sleep loss in adolescents.

LEAD AUTHOR

Judith A. Owens, MD, FAAP

ADOLESCENT SLEEP WORKING GROUP

Rhoda Au, PhD
Mary Carskadon, PhD
Richard Millman, MD
Amy Wolfson, PhD

COMMITTEE ON ADOLESCENCE 2012–2013

Paula K. Braverman, MD, FAAP, Chairperson
William P. Adelman, MD, FAAP
Cora C. Breuner, MD, MPH, FAAP
David A. Levine, MD, FAAP
Arik V. Marcell, MD, MPH, FAAP
Pamela J. Murray, MD, MPH, FAAP
Rebecca F. O'Brien, MD, FAAP

LIAISONS

Loretta E. Gavin, PhD, MPH – *Centers for Disease Control and Prevention*
Rachel J. Miller, MD – *American College of Obstetricians and Gynecologists*
Margo Lane, MD, FAAP – *Canadian Pediatric Society*
Benjamin Shain, MD, PhD – *American Academy of Child and Adolescent Psychiatry*

STAFF

Karen Smith
James Baumberger, MPP

REFERENCES

1. Millman RP; Working Group on Sleepiness in Adolescents/Young Adults; AAP Committee on Adolescence. Excessive sleepiness in adolescents and young adults: causes, consequences, and treatment strategies. *Pediatrics*. 2005;115(6):1774–1786
2. American Medical Association, American Academy of Sleep Medicine. *Resolution 503: Insufficient Sleep in Adolescents*. Chicago, IL: American Medical Association, American Academy of Sleep Medicine; 2010
3. Sleep Health. Healthy People 2020 topics and objectives. Available at: www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=38. Accessed November 14, 2013
4. National Sleep Foundation. 2006 Teens and sleep. Sleep in America Polls. Washington, DC: National Sleep Foundation; 2006. Available at: www.sleepfoundation.org/article/sleep-america-polls/2006-teens-and-sleep. Accessed November 14, 2013
5. Huang YS, Wang CH, Guilleminault C. An epidemiologic study of sleep problems among adolescents in North Taiwan. *Sleep Med*. 2010;11(10):1035–1042
6. Yang CK, Kim JK, Patel SR, Lee JH. Age-related changes in sleep/wake patterns among Korean teenagers. *Pediatrics*. 2005;115(suppl 1):250–256
7. Brand S, Hatzinger M, Beck J, Holsboer-Trachsler E. Perceived parenting styles, personality traits and sleep patterns in adolescents. *J Adolesc*. 2009;32(5):1189–1207
8. Pallesen S, Saxvig IW, Molde H, Sørensen E, Wilhelmsen-Langeland A, Bjorvatn B. Brief report: behaviorally induced insufficient sleep syndrome in older adolescents: prevalence and correlates. *J Adolesc*. 2011;34(2):391–395
9. Pérez A, Roberts RE, Sanderson M, Reininger B, Aguirre-Flores MI. Disturbed sleep among adolescents living in 2 communities on the Texas-Mexico border, 2000-2003. *Prev Chronic Dis*. 2010;7(2):A40
10. Lund HG, Reider BD, Whiting AB, Prichard JR. Sleep patterns and predictors of disturbed sleep in a large population of college students. *J Adolesc Health*. 2010;46(2):124–132
11. Urner M, Tornic J, Bloch KE. Sleep patterns in high school and university students: a longitudinal study. *Chronobiol Int*. 2009;26(6):1222–1234
12. Arora T, Broglia E, Pushpakumar D, et al. An investigation into the strength of the association and agreement levels between subjective and objective sleep duration in adolescents. *PloS One*. 2013;8(8):e72406
13. Eaton DK, McKnight-Eily LR, Lowry R, Perry GS, Presley-Cantrell L, Croft JB. Prevalence of insufficient, borderline, and optimal hours of sleep among high school students—United States, 2007. *J Adolesc Health*. 2010;46(4):399–401
14. Loessl B, Valerius G, Kopasz M, Hornyak M, Riemann D, Voderholzer U. Are adolescents chronically sleep-deprived? An investigation of sleep habits of adolescents in the southwest of Germany. *Child Care Health Dev*. 2008;34(5):549–556
15. Noland H, Price JH, Dake J, Telljohann SK. Adolescents' sleep behaviors and perceptions of sleep. *J Sch Health*. 2009;79(5):224–230
16. Knutson KL, Lauderdale DS. Sociodemographic and behavioral predictors of bed time and wake time among US adolescents aged 15 to 17 years. *J Pediatr*. 2009;154(3):426–430, 430.e1
17. Gupta R, Bhatia MS, Chhabra V, et al. Sleep patterns of urban school-going adolescents. *Indian Pediatr*. 2008;45(3):183–189
18. Olds T, Maher C, Blunden S, Matricciani L. Normative data on the sleep habits of Australian children and adolescents. *Sleep*. 2010;33(10):1381–1388
19. Patel NP, Grandner MA, Xie D, Branas CC, Gooneratne N. "Sleep disparity" in the population: poor sleep quality is strongly associated with poverty and ethnicity. *BMC Public Health*. 2010;10:475
20. Spilsbury JC, Storfer-Isser A, Drotar D, et al. Sleep behavior in an urban US sample of school-aged children. *Arch Pediatr Adolesc Med*. 2004;158(10):988–994
21. Dollman J, Ridley K, Olds T, Lowe E. Trends in the duration of school-day sleep among 10- to 15-year-old South Australians between 1985 and 2004. *Acta Paediatr*. 2007;96(7):1011–1014
22. Moore M, Kirchner HL, Drotar D, Johnson N, Rosen C, Redline S. Correlates of adolescent sleep time and variability in sleep time: the role of individual and health related characteristics. *Sleep Med*. 2011;12(3):239–245
23. Marco CA, Wolfson AR, Sparling M, Azuaje A. Family socioeconomic status and sleep patterns of young adolescents. *Behav Sleep Med*. 2011;10(1):70–80
24. Dodor BA, Shelley MC, Hausafus CO. Adolescents' health behaviors and obesity: does race affect this epidemic? *Nutr Res Pract*. 2010;4(6):528–534
25. Daniel LC, Boergers J, Kopel SJ, Koinis-Mitchell D. Missed sleep and asthma morbidity in urban children. *Ann Allergy Asthma Immunol*. 2012;109(1):41–46
26. McHale SM, Kim JY, Kan M, Updegraff KA. Sleep in Mexican-American adolescents: social ecological and well-being correlates. *J Youth Adolesc*. 2011;40(6):666–679
27. Clinkinbeard SS, Simi P, Evans MK, Anderson AL. Sleep and delinquency: does the amount of sleep matter? *J Youth Adolesc*. 2011;40(7):916–930
28. Mednick SC, Christakis NA, Fowler JH. The spread of sleep loss influences drug use in adolescent social networks. *PLoS ONE*. 2010;5(3):e9775
29. Gau SS, Soong WT, Merikangas KR. Correlates of sleep-wake patterns among children and young adolescents in Taiwan. *Sleep*. 2004;27(3):512–519
30. Randler C, Bilger S. Associations among sleep, chronotype, parental monitoring, and pubertal development among German adolescents. *J Psychol*. 2009;143(5):509–520
31. Majori S, Pasqualetto C, Mantovani W, et al. Self-reported sleep disorders in secondary school students: an epidemiological and risk behavioural analysis. *J Prev Med Hyg*. 2009;50(2):102–108
32. Singleton RA, Jr, Wolfson AR. Alcohol consumption, sleep, and academic performance among college students. *J Stud Alcohol Drugs*. 2009;70(3):355–363
33. Danner F, Phillips B. Adolescent sleep, school start times, and teen motor vehicle crashes. *J Clin Sleep Med*. 2008;4(6):533–535
34. Roberts RE, Roberts CR, Duong HT. Sleepless in adolescence: prospective data on sleep deprivation, health and functioning. *J Adolesc*. 2009;32(5):1045–1057
35. Glozier N, Martiniuk A, Patton G, et al. Short sleep duration in prevalent and persistent psychological distress in young adults: the DRIVE study. *Sleep*. 2010;33(9):1139–1145
36. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. *Sleep*. 1993;16(3):258–262
37. Roenneberg T, Kuehnle T, Pramstaller PP, et al. A marker for the end of adolescence. *Curr Biol*. 2004;14(24):R1038–R1039
38. Jenni OG, Achermann P, Carskadon MA. Homeostatic sleep regulation in adolescents. *Sleep*. 2005;28(11):1446–1454
39. Taylor DJ, Jenni OG, Acebo C, Carskadon MA. Sleep tendency during extended wakefulness: insights into adolescent

sleep regulation and behavior. *J Sleep Res*. 2005;14(3):239–244

40. Cain N, Gradisar M. Electronic media use and sleep in school-aged children and adolescents: a review. *Sleep Med*. 2010;11(8):735–742
41. Crowley SJ, Carskadon MA. Modifications to weekend recovery sleep delay circadian phase in older adolescents. *Chronobiol Int*. 2010;27(7):1469–1492
42. Calamaro CJ, Mason TB, Ratcliffe SJ. Adolescents living the 24/7 lifestyle: effects of caffeine and technology on sleep duration and daytime functioning. *Pediatrics*. 2009;123(6). Available at: www.pediatrics.org/cgi/content/full/123/6/e1005
43. Munezawa T, Kaneita Y, Osaki Y, et al. The association between use of mobile phones after lights out and sleep disturbances among Japanese adolescents: a nationwide cross-sectional survey. *Sleep*. 2011;34(8):1013–1020
44. Shochat T, Flint-Bretler O, Tzischinsky O. Sleep patterns, electronic media exposure and daytime sleep-related behaviours among Israeli adolescents. *Acta Paediatr*. 2010;99(9):1396–1400
45. Eggermont S, Van den Bulck J. Nodding off or switching off? The use of popular media as a sleep aid in secondary-school children. *J Paediatr Child Health*. 2006;42(7–8):428–433
46. Van den Bulck J. Television viewing, computer game playing, and Internet use and self-reported time to bed and time out of bed in secondary-school children. *Sleep*. 2004;27(1):101–104
47. Johnson JG, Cohen P, Kasen S, First MB, Brook JS. Association between television viewing and sleep problems during adolescence and early adulthood. *Arch Pediatr Adolesc Med*. 2004;158(6):562–568
48. Higuchi S, Motohashi Y, Liu Y, Maeda A. Effects of playing a computer game using a bright display on presleep physiological variables, sleep latency, slow wave sleep and REM sleep. *J Sleep Res*. 2005;14(3):267–273
49. Punamäki RL, Wallenius M, Nygård CH, Saarni L, Rimpelä A. Use of information and communication technology (ICT) and perceived health in adolescence: the role of sleeping habits and waking-time tiredness. *J Adolesc*. 2007;30(4):569–585
50. Choi K, Son H, Park M, et al. Internet overuse and excessive daytime sleepiness in adolescents. *Psychiatry Clin Neurosci*. 2009;63(4):455–462
51. Dworak M, Schierl T, Bruns T, Strüder HK. Impact of singular excessive computer game and television exposure on sleep patterns and memory performance of school-aged children. *Pediatrics*. 2007;120(5):978–985
52. Carskadon MA, Acebo C. Regulation of sleepiness in adolescents: update, insights, and speculation. *Sleep*. 2002;25(6):606–614
53. Van den Bulck J. Adolescent use of mobile phones for calling and for sending text messages after lights out: results from a prospective cohort study with a one-year follow-up. *Sleep*. 2007;30(9):1220–1223
54. Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose-response relationships for resetting of human circadian clock by light. *Nature*. 1996;379(6565):540–542
55. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol*. 2000;526(pt 3):695–702
56. Higuchi S, Motohashi Y, Liu Y, Ahara M, Kaneko Y. Effects of VDT tasks with a bright display at night on melatonin, core temperature, heart rate, and sleepiness. *J Appl Physiol (1985)*. 2003;94(5):1773–1776
57. Wolfson AR, Carskadon MA. A survey of factors influencing high school start times. *NASSP Bull*. 2005;89(642):47–66
58. American Academy of Pediatrics, Adolescent Sleep Working Group, Committee on Adolescence, and Council on School Health. School start times for adolescents. *Pediatrics*. 2014;134(3)
59. Carskadon MA, Wolfson AR, Acebo C, Tzischinsky O, Seifer R. Adolescent sleep patterns, circadian timing, and sleepiness at a transition to early school days. *Sleep*. 1998;21(8):871–881
60. Wahlstrom K. Changing times: findings from the first longitudinal study of later high school start times. *NASSP Bull*. 2002;86(633):3–21
61. Dexter D, Bijwadia J, Schilling D, Applebaugh G. Sleep, sleepiness and school start times: a preliminary study. *WMJ*. 2003;102(1):44–46
62. Owens JA, Belon K, Moss P. Impact of delaying school start time on adolescent sleep, mood, and behavior. *Arch Pediatr Adolesc Med*. 2010;164(7):608–614
63. Epstein R, Chillag N, Lavie P. Starting times of school: effects on daytime functioning of fifth-grade children in Israel. *Sleep*. 1998;21(3):250–256
64. Wolfson AR, Spaulding NL, Dandrow C, Baroni EM. Middle school start times: the importance of a good night's sleep for young adolescents. *Behav Sleep Med*. 2007;5(3):194–209
65. Lufi D, Tzischinsky O, Hadar S. Delaying school starting time by one hour: some effects on attention levels in adolescents. *J Clin Sleep Med*. 2011;7(2):137–143
66. Vorona RD, Szklo-Coxe M, Wu A, Dubik M, Zhao Y, Ware JC. Dissimilar teen crash rates in two neighboring southeastern Virginia cities with different high school start times. *J Clin Sleep Med*. 2011;7(2):145–151
67. Kristjansson AL, Sigfusdottir ID, Allegrante JP, James JE. Adolescent caffeine consumption, daytime sleepiness and anger. *J Caffeine Res*. 2011;1(1):75–82
68. Bryant Ludden A, Wolfson AR. Understanding adolescent caffeine use: connecting use patterns with expectancies, reasons, and sleep. *Health Educ Behav*. 2010;37(3):330–342
69. Pollak CP, Bright D. Caffeine consumption and weekly sleep patterns in US seventh-, eighth-, and ninth-graders. *Pediatrics*. 2003;111(1):42–46
70. Reissig CJ, Strain EC, Griffiths RR. Caffeinated energy drinks—a growing problem. *Drug Alcohol Depend*. 2009;99(1–3):1–10
71. Orbeta RL, Overpeck MD, Ramcharran D, Kogan MD, Ledsky R. High caffeine intake in adolescents: associations with difficulty sleeping and feeling tired in the morning. *J Adolesc Health*. 2006;38(4):451–453
72. Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. *Sleep Med Rev*. 2008;12(2):153–162
73. Gromov I, Gromov D. Sleep and substance use and abuse in adolescents. *Child Adolesc Psychiatr Clin N Am*. 2009;18(4):929–946
74. O'Dea JA. Consumption of nutritional supplements among adolescents: usage and perceived benefits. *Health Educ Res*. 2003;18(1):98–107
75. Bernstein GA, Carroll ME, Thuras PD, Cosgrove KP, Roth ME. Caffeine dependence in teenagers. *Drug Alcohol Depend*. 2002;66(1):1–6
76. Strain EC, Griffiths RR. Caffeine dependence: fact or fiction? *J R Soc Med*. 1995;88(8):437–440
77. Collins L, Graham JW, Rousculp SS, Hansen W. Heavy caffeine use and the beginning of the substance use onset process: an illustration of latent analysis. In: Bryant KJ, Windle M, West SG, eds. *The Science of Prevention: Methodological Advances from Alcohol and Substance Abuse Research*. Washington, DC: American Psychological Association; 1997:79–99
78. Miller MC. What are caffeine's psychological benefits and risks? *Harv Ment Health Lett*. 2005;22(3):8
79. Tennant FS, Jr, Detels R. Relationship of alcohol, cigarette, and drug abuse in

adulthood with alcohol, cigarette and coffee consumption in childhood. *Prev Med*. 1976;5(1):70–77

80. Martin CA, Cook C, Woodring JH, et al. Caffeine use: association with nicotine use, aggression, and other psychopathology in psychiatric and pediatric outpatient adolescents. *ScientificWorldJournal*. 2008; 8:512–516
81. Jaehne A, Loessl B, Bárkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev*. 2009; 13(5):363–377
82. James JE, Kristjánsson AL, Sigfúsdóttir ID. Adolescent substance use, sleep, and academic achievement: evidence of harm due to caffeine. *J Adolesc*. 2011;34(4):665–673
83. Whalen DJ, Silk JS, Semel M, et al. Caffeine consumption, sleep, and affect in the natural environments of depressed youth and healthy controls. *J Pediatr Psychol*. 2008;33(4):358–367
84. Marczinski CA, Fillmore MT, Henges AL, Ramsey MA, Young CR. Effects of energy drinks mixed with alcohol on information processing, motor coordination and subjective reports of intoxication. *Exp Clin Psychopharmacol*. 2012;20(2):129–138
85. Lookatch SJ, Dunne EM, Katz EC. Predictors of nonmedical use of prescription stimulants. *J Psychoactive Drugs*. 2012;44 (1):86–91
86. Garnier-Dykstra LM, Caldeira KM, Vincent KB, O'Grady KE, Arria AM. Nonmedical use of prescription stimulants during college: four-year trends in exposure opportunity, use, motives, and sources. *J Am Coll Health*. 2012;60(3):226–234
87. Berkey CS, Rockett HR, Colditz GA. Weight gain in older adolescent females: the internet, sleep, coffee, and alcohol. *J Pediatr*. 2008;153(5):635–639, 639.e1
88. Harrison Y, Horne JA. The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl*. 2000;6(3):236–249
89. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. *Pediatr Clin North Am*. 2011;58(3):649–665
90. Chen MC, Burley HW, Gotlib IH. Reduced sleep quality in healthy girls at risk for depression. *J Sleep Res*. 2012;21(1):68–72
91. Howland RH. Sleep interventions for the treatment of depression. *J Psychosoc Nurs Ment Health Serv*. 2011;49(1):17–20
92. Okun ML, Luther J, Prather AA, Perel JM, Wisniewski S, Wisner KL. Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. *J Affect Disord*. 2011;130(3):378–384
93. Lofthouse N, Gilchrist R, Splaingard M. Mood-related sleep problems in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 2009;18(4):893–916
94. Dahl RE, Ryan ND, Matty MK, et al. Sleep onset abnormalities in depressed adolescents. *Biol Psychiatry*. 1996;39(6):400–410
95. Lopez J, Hoffmann R, Armitage R. Reduced sleep spindle activity in early-onset and elevated risk for depression. *J Am Acad Child Adolesc Psychiatry*. 2010;49(9):934–943
96. Regestein Q, Natarajan V, Pavlova M, Kawasaki S, Gleason R, Koff E. Sleep debt and depression in female college students. *Psychiatry Res*. 2010;176(1):34–39
97. O'Brien EM, Mindell JA. Sleep and risk-taking behavior in adolescents. *Behav Sleep Med*. 2005;3(3):113–133
98. Catrett CD, Gaultney JF. Possible insomnia predicts some risky behaviors among adolescents when controlling for depressive symptoms. *J Genet Psychol*. 2009; 170(4):287–309
99. Coulombe JA, Reid GJ, Boyle MH, Racine Y. Concurrent associations among sleep problems, indicators of inadequate sleep, psychopathology, and shared risk factors in a population-based sample of healthy Ontario children. *J Pediatr Psychol*. 2010; 35(7):790–799
100. Hasler G, Buysse DJ, Klaghofer R, et al. The association between short sleep duration and obesity in young adults: a 13-year prospective study. *Sleep*. 2004;27(4):661–666
101. Liu X. Sleep and adolescent suicidal behavior. *Sleep*. 2004;27(7):1351–1358
102. Liu X, Buysse DJ. Sleep and youth suicidal behavior: a neglected field. *Curr Opin Psychiatry*. 2006;19(3):288–293
103. An H, Ahn JH, Bhang SY. The association of psychosocial and familial factors with adolescent suicidal ideation: a population-based study. *Psychiatry Res*. 2010;177(3): 318–322
104. Fitzgerald CT, Messias E, Buysse DJ. Teen sleep and suicidality: results from the youth risk behavior surveys of 2007 and 2009. *J Clin Sleep Med*. 2011;7(4):351–356
105. Leproult R, Van Cauter E. Role of sleep and sleep loss in hormonal release and metabolism. *Endocr Dev*. 2010;17:11–21
106. Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. *Sleep Med*. 2008;9(9 suppl 1): S23–S28
107. Van Cauter E, Knutson KL. Sleep and the epidemic of obesity in children and adults. *Eur J Endocrinol*. 2008;159(suppl 1):S59–S66
108. Countryman AJ, Saab PG, Llabre MM, Penedo FJ, McCalla JR, Schneiderman N. Cardiometabolic risk in adolescents: associations with physical activity, fitness, and sleep. *Ann Behav Med*. 2013;45(1):121–131
109. Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. *Sleep*. 2008;31(5):619–626
110. Gupta NK, Mueller WH, Chan W, Meininger JC. Is obesity associated with poor sleep quality in adolescents? *Am J Hum Biol*. 2002;14(6):762–768
111. Seicean A, Redline S, Seicean S, et al. Association between short sleeping hours and overweight in adolescents: results from a US suburban high school survey. *Sleep Breath*. 2007;11(4):285–293
112. Liou YM, Liou TH, Chang LC. Obesity among adolescents: sedentary leisure time and sleeping as determinants. *J Adv Nurs*. 2010;66(6):1246–1256
113. Snell EK, Adam EK, Duncan GJ. Sleep and the body mass index and overweight status of children and adolescents. *Child Dev*. 2007;78(1):309–323
114. Al Mamun A, Lawlor DA, Cramb S, O'Callaghan M, Williams G, Najman J. Do childhood sleeping problems predict obesity in young adulthood? Evidence from a prospective birth cohort study. *Am J Epidemiol*. 2007; 166(12):1368–1373
115. Matthews KA, Dahl RE, Owens JF, Lee L, Hall M. Sleep duration and insulin resistance in healthy black and white adolescents. *Sleep*. 2012;35(10):1353–1358
116. Al-Disi D, Al-Daghri N, Khanam L, et al. Subjective sleep duration and quality influence diet composition and circulating adipocytokines and ghrelin levels in teenage girls. *Endocr J*. 2010;57(10):915–923
117. Weiss A, Xu F, Storfer-Isser A, Thomas A, levers-Landis CE, Redline S. The association of sleep duration with adolescents' fat and carbohydrate consumption. *Sleep*. 2010;33(9):1201–1209
118. Martinez-Gomez D, Eisenmann JC, Gomez-Martinez S, et al; AFINOS Study Group. Sleep duration and emerging cardiometabolic risk markers in adolescents. The AFINOS study. *Sleep Med*. 2011;12(10):997–1002
119. Beebe DW, Lewin D, Zeller M, et al. Sleep in overweight adolescents: shorter sleep, poorer sleep quality, sleepiness, and sleep-disordered breathing. *J Pediatr Psychol*. 2007;32(1):69–79
120. Kang KT, Chou CH, Weng WC, Lee PL, Hsu WC. Associations between adenotonsillar hypertrophy, age, and obesity in children with obstructive sleep apnea. *PLoS One*. 2013;8(10):e78666

121. Kheirandish-Gozal L, Etzioni T, Bhattacharjee R, et al. Obstructive sleep apnea in children is associated with severity-dependent deterioration in overnight endothelial function. *Sleep Med*. 2013;14(6):526–531
122. Van Hoorenbeeck K, Franckx H, Debode Pet al. Metabolic disregulation in obese adolescents with sleep-disordered breathing before and after weight loss. *Obesity (Silver Spring)*. 2013;21(7):1446–1450
123. Ingram DG, Matthews CK. Effect of adenotonsillectomy on C-reactive protein levels in children with obstructive sleep apnea: a meta-analysis. *Sleep Med*. 2013;14(2):172–176
124. Knutson KL. Sex differences in the association between sleep and body mass index in adolescents. *J Pediatr*. 2005;147(6):830–834
125. Sun Y, Sekine M, Kagamimori S. Lifestyle and overweight among Japanese adolescents: the Toyama birth cohort study. *J Epidemiol*. 2009;19(6):303–310
126. Calamaro CJ, Park S, Mason TB, et al. Shortened sleep duration does not predict obesity in adolescents. *J Sleep Res*. 2010;19(4):559–566
127. Knutson KL, Lauderdale DS. Sleep duration and overweight in adolescents: self-reported sleep hours versus time diaries. *Pediatrics*. 2007;119(5). Available at: www.pediatrics.org/cgi/content/full/119/5/e1056
128. Garbarino S, Nobili L, Beelke M, De Carli F, Ferrillo F. The contributing role of sleepiness in highway vehicle accidents. *Sleep*. 2001;24(2):203–206
129. Connor J, Whitlock G, Norton R, Jackson R. The role of driver sleepiness in car crashes: a systematic review of epidemiological studies. *Accid Anal Prev*. 2001;33(1):31–41
130. Connor J, Norton R, Ameratunga S, et al. Driver sleepiness and risk of serious injury to car occupants: population based case control study. *BMJ*. 2002;324(7346):1125
131. Philip P, Akerstedt T. Transport and industrial safety, how are they affected by sleepiness and sleep restriction? *Sleep Med Rev*. 2006;10(5):347–356
132. Pack AI, Pack AM, Rodgman E, Cucchiara A, Dinges DF, Schwab CW. Characteristics of crashes attributed to the driver having fallen asleep. *Accid Anal Prev*. 1995;27(6):769–775
133. Lowden A, Anund A, Kecklund G, Peters B, Akerstedt T. Wakefulness in young and elderly subjects driving at night in a car simulator. *Accid Anal Prev*. 2009;41(5):1001–1007
134. Åkerstedt T, Kecklund G. Age, gender and early morning highway accidents. *J Sleep Res*. 2001;10(2):105–110
135. Hutchens L, Senserrick TM, Jamieson PE, Romer D, Winston FK. Teen driver crash risk and associations with smoking and drowsy driving. *Accid Anal Prev*. 2008;40(3):869–876
136. Pizza F, Contardi S, Antognini AB, et al. Sleep quality and motor vehicle crashes in adolescents. *J Clin Sleep Med*. 2010;6(1):41–45
137. Taylor DJ, Bramoweth AD. Patterns and consequences of inadequate sleep in college students: substance use and motor vehicle accidents. *J Adolesc Health*. 2010;46(6):610–612
138. Sagaspe P, Taillard J, Chaumet G, Moore N, Bioulac B, Philip P. Aging and nocturnal driving: better with coffee or a nap? A randomized study. *Sleep*. 2007;30(12):1808–1813
139. Smith-Coggins R, Howard SK, Mac DT, et al. Improving alertness and performance in emergency department physicians and nurses: the use of planned naps. *Ann Emerg Med*. 2006;48(5):596–604, 604.e1–e3

Insufficient Sleep in Adolescents and Young Adults: An Update on Causes and Consequences

Judith Owens, ADOLESCENT SLEEP WORKING GROUP and COMMITTEE ON ADOLESCENCE

Pediatrics 2014;134;e921
DOI: 10.1542/peds.2014-1696 originally published online August 25, 2014;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Insufficient Sleep in Adolescents and Young Adults: An Update on Causes and Consequences

Judith Owens, ADOLESCENT SLEEP WORKING GROUP and COMMITTEE ON ADOLESCENCE

Pediatrics 2014;134;e921
DOI: 10.1542/peds.2014-1696 originally published online August 25, 2014;

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1306722.

Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado

Lisa M. McKenzie,[1] Ruixin Guo,[2] Roxana Z. Witter,[1] David A. Savitz,[3] Lee S. Newman,[1] and John L. Adgate[1]

[1]Department of Environmental and Occupational Health, and [2]Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, Colorado, USA; [3]Department of Epidemiology, Brown University, Providence, Rhode Island, USA

Background: Birth defects are a leading cause of neonatal mortality. Natural gas development (NGD) emits several potential teratogens, and U.S. production of natural gas is expanding.

Objectives: We examined associations between maternal residential proximity to NGD and birth outcomes in a retrospective cohort study of 124,842 births between 1996 and 2009 in rural Colorado.

Methods: We calculated inverse distance weighted natural gas well counts within a 10-mile radius of maternal residence to estimate maternal exposure to NGD. Logistic regression, adjusted for maternal and infant covariates, was used to estimate associations with exposure tertiles for congenital heart defects (CHDs), neural tube defects (NTDs), oral clefts, preterm birth, and term low birth weight. The association with term birth weight was investigated using multiple linear regression.

Results: Prevalence of CHDs increased with exposure tertile, with an odds ratio (OR) of 1.3 for the highest tertile (95% CI: 1.2, 1.5); NTD prevalence was associated with the highest tertile of exposure (OR = 2.0; 95% CI: 1.0, 3.9, based on 59 cases), compared with the absence of any gas wells within a 10-mile radius. Exposure was negatively associated with preterm birth and positively associated with fetal growth, although the magnitude of association was small. No association was found between exposure and oral clefts.

Conclusions: In this large cohort, we observed an association between density and proximity of natural gas wells within a 10-mile radius of maternal residence and prevalence of CHDs and possibly NTDs. Greater specificity in exposure estimates is needed to further explore these associations.

Citation: McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. 2014. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect 122:412–417; http://dx.doi.org/10.1289/ehp.1306722

Introduction

Approximately 3.3% of U.S. live-born children have a major birth defect (Centers for Disease Control and Prevention 2013; Parker et al. 2010); these defects account for 20% of infant deaths as well as 2.3% of premature death and disability (McKenna et al. 2005). Oral clefts, neural tube defects (NTDs), and congenital heart defects (CHD) are the most common classes of birth defects (Parker et al. 2010). These defects are thought to originate in the first trimester as a result of polygenic inherited disease or gene–environment interactions (Brent 2004). Suspected nongenetic risk factors for these birth defects include folate deficiency (Wald and Sneddon 1991), maternal smoking (Honein et al. 2006), alcohol abuse and solvent use (Romitti et al. 2007), and exposure to benzene (Lupo et al. 2010b; Wennborg et al. 2005), toluene (Bowen et al. 2009), polycyclic aromatic hydrocarbons (PAHs) (Ren et al. 2011), and petroleum-based solvents, including aromatic hydrocarbons (Chevrier et al. 1996). Associations between air pollution [volatile organic compounds (VOCs), particulate matter (PM), and nitrogen dioxide (NO_2)] and low birth weight and preterm birth have been reported (Ballester et al. 2010; Brauer et al. 2008; Dadvand et al. 2013; Ghosh et al. 2012; Llop et al. 2010). Many of these air pollutants are emitted during development and production of natural gas (referred to herein as NGD), and concerns have been raised that they may increase risk of adverse birth outcomes and other health effects (Colborn et al. 2011; McKenzie et al. 2012). Increased prevalence of low birth weight and small for gestational age and reduced APGAR scores were reported in infants born to mothers living near NGD in Pennylvania (Hill 2013).

Technological advances in directional drilling and hydraulic fracturing have resulted in a global boom of drilling and production of natural gas reserves [U.S. Energy Information Administration (EIA) 2011a, 2011b; Vidas and Hugman 2008]. NGD is an industrial process resulting in potential worker and community exposure to multiple environmental stressors (Esswein et al. 2013; King 2012; Witter et al. 2013). Diesel-powered heavy equipment is used for worksite development as well as transporting large volumes of water, sand, and chemicals to sites and for waste removal (Witter et al. 2013). It is increasingly common for NGD to encroach on populated areas, potentially exposing more people to air and water emissions as well as to noise and community-level changes that may arise from industrialization [Colorado Oil and Gas Conservation Commission (COGCC) 2009]. Studies in Colorado, Texas, Wyoming, and Oklahoma have demonstrated that NGD results in emission of VOCs, NO_2, sulfur dioxide (SO_2), PM, and PAHs from either the well itself or from associated drilling processes or related infrastructure (i.e., drilling muds, hydraulic fracturing fluids, tanks containing waste water and liquid hydrocarbons, diesel engines, compressor stations, dehydrators, and pipelines) (CDPHE 2007; Frazier 2009; Kemball-Cook et al. 2010; Olaguer 2012; Walther 2011; Zielinska et al. 2011). Some of these pollutants, such as toluene, xylenes, and benzene, are suspected teratogens (Lupo et al. 2010b; Shepard 1995) or mutagens (Agency for Toxic Substances and Disease Registry 2007) and are known to cross the placenta (Bukowski 2001), raising the possibility of fetal exposure to these and other pollutants resulting from NGD. Currently, there are few studies on the effects of air pollution or NGD on birth outcomes.

In this analysis, we explored the association between maternal exposure to NGD and birth outcomes, using a data set with individual-level birth data and geocoded natural gas well locations. We conducted a retrospective cohort study to investigate the association between density and proximity of natural gas wells within a 10-mile radius of maternal residences in rural Colorado and three classes of birth defects, preterm birth, and fetal growth.

Methods

Study population. We used information available in the publically accessible Colorado Oil and Gas Information System (COGIS) to

Address correspondence to L. McKenzie, Department of Environmental and Occupational Health, Colorado School of Public Health, 13001 E. 17th Pl., Campus Box B119, Aurora, CO 80045 USA. Telephone: (303) 724-5557. E-mail: Lisa.McKenzie@ucdenver.edu

Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1306722).

This study was supported by the Department of Environmental and Occupational Health at the Colorado School of Public Health. The Colorado Department of Public Health and Environment's (CDPHE) Health Statistics and Colorado Responds to Children with Special Needs provided outcome data for this study.

The CDPHE specifically disclaims responsibility for any analyses, interpretations, or conclusions.

The authors declare they have no actual or potential competing financial interests.

Received: 27 February 2013; Accepted: 28 January 2014; Advance Publication: 28 January 2014; Final Publication: 1 April 2014.

build a geocoded data set with latitude, longitude, and year of development (1996–2009) for all gas wells in rural Colorado (COGIS 2011). Live birth data were obtained from the Colorado Vital Birth Statistics (CDPHE, Denver, CO). Geocoded maternal addresses at time of birth were linked to the well locations. Distance of each maternal residence from all existing (not abandoned) natural gas wells within a 10-mile radius was then computed using spherically adjusted straight line distances. We conducted our analysis on the final de-identified database containing maternal and birth outcome data described below and distance to all wells within the 10-mile radius. The Colorado Multiple Institutional Review Board reviewed and approved our study protocol. Informed consent was not required.

We restricted analysis to births occurring from 1996 through 2009 to focus our analysis on growth of unconventional NGD, characterized by use of hydraulic fracturing and/or directional drilling (King 2012), which expanded rapidly in Colorado beginning around 2000 (COGIS 2011). We also restricted our analysis to rural areas and towns with populations of < 50,000 (excluding the Denver metropolitan area, El Paso County, and the cities of Fort Collins, Boulder, Pueblo, Grand Junction, and Greeley) in 57 counties to reduce potential for exposure to other pollution sources, such as traffic, congestion, and industry. The final study area included locations with and without NGD. We conducted a retrospective study on the resulting cohort of 124,842 live births to explore associations between birth outcomes and exposure to NGD operations. We restricted eligibility to singleton births and excluded the small proportion (< 5%) of nonwhite births because there were too few to analyze separately.

Birth outcomes. Identified birth outcomes were *a*) oral cleft, including cleft lip with and without cleft palate as well as cleft palate [*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 749.xx] (National Center for Health Statistics 2011); *b*) NTD, including anencephalus, spina bifida without anecephaly, and encephalocele (ICD-9-CM 740.xx, 741.xx, and 742.0); *c*) CHD, including transposition of great vessels, tetralogy of Fallot, ventricular septal defect, endocardial cushion defect, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, Ebstein's anomaly, aortic valve stenosis, hypoplastic left heart syndrome, patent ductus arteriosis, coarctation of aorta, and pulmonary artery anomalies (codes 745.xx, 746.xx, 747.xx, excluding 746.9, 747.5); *d*) preterm birth (< 37 weeks completed gestation); *e*) term low birth weight (≥ 37 weeks completed gestation and birth weight < 2,500 g); and *f*) term birth weight as a continuous measure. Births with an oral cleft, NTD, or CHD were excluded from preterm birth and term low birth weight analysis. Preterm births were excluded from term birth weight analysis. Oral cleft, CHD, and NTD cases in the Colorado Responds to Children with Special Needs (CRCSN) birth registry, obtained from hospital records, the Newborn Genetics Screening Program, the Newborn Hearing Screening Program, laboratories, physicians, and genetic, developmental, and other specialty clinics (CRCSN 2011) were matched with Colorado live birth certificates. Cases are reflective of reporting as of 12 July 2012, were not necessarily confirmed by medical record review, and are subject to change as CRCSN ascertains diagnosis up to 3 years of child's age and/or supplements information by medical record review. We analyzed birth defects in three heterogeneous groups to increase statistical power. Data set information was not sufficient to distinguish between multiple and isolated birth anomalies or to identify chromosomal birth anomalies. In an exploratory analysis, we considered seven clinical diagnostic groupings of CHDs: *a*) conotruncal defects (tetralogy of Fallot and transposition of great vessels); *b*) endocardial cushion and mitrovalve defects (EMD; endocardial cushion defect and hypoplastic left heart syndrome); *c*) pulmonary artery and valve defects (PAV; pulmonary valve atresia and stenosis and pulmonary artery anomalies); *d*) tricuspid valve defects (TVD; tricuspid valve atresia and stenosis and Ebstein's anomaly); *e*) aortic artery and valve defects (aortic valve stenosis and coarctation of aorta); *f*) ventricular septal defects (VSD); and *g*) patent ductus arteriosis in births > 2,500 g (Gilboa et al. 2005).

Exposure assessment. Distribution of the wells within a 10-mile radius of maternal residence shows 50% and 90% of wells to be within 2.3 and 7.7 miles of maternal residence, respectively. We used an inverse distance weighted (IDW) approach, commonly used to estimate individual air pollutant exposures from multiple fixed locations (Brauer et al. 1998; Ghosh et al. 2012), to estimate maternal exposure. Our IDW well count accounts for the number of wells within the 10-mile radius of the maternal residence, as well as distance of each well from the maternal residence, giving greater weight to wells closest to the maternal residence. For example, an IDW well count of 125 wells/mile could be computed from 125 wells each located 1 mile from the maternal residence or 25 wells each located 0.2 miles from the maternal residence. We calculated the IDW well count of all existing natural gas wells in the birth year within a 10-mile radius of each maternal residence as a continuous exposure metric:

$$\text{IDW well count} = \sum_{i=1}^{n} \frac{1}{d_i}, \qquad [1]$$

where IDW well count is the IDW count of existing wells within a 10-mile radius of maternal residence in the birth year; d_i is the distance of the ith individual well from maternal residence; and n is the number of existing wells within a 10-mile radius of maternal residence in the birth year.

The IDW well count was calculated for each maternal residence with ≥ 1 gas wells within 10 miles. The final distribution then was divided into tertiles (low, medium, and high) for subsequent logistic and linear regression analysis. Each tertile was compared with the referent group (no natural gas wells within 10 miles, IDW well count = 0).

Statistical analysis. We used logistic regressions to study associations between each dichotomous outcome and IDW exposure group. We also considered term birth weight as a continuous outcome using multiple linear regression. First, we estimated the crude odds ratio (OR) associated with IDW exposure tertile for each binary outcome, followed by a Cochran–Armitage test to evaluate linear trends in binominal proportions with increasing IDW exposure (none, low, medium, and high). We further investigated associations by adjusting for potential confounders, as well as infant and maternal covariates selected based on both *a priori* knowledge and empirical consideration of their association with exposure and an outcome. Specifically, covariates in our analysis of all outcomes except outcomes with very few events (i.e., NTDs, conotruncal defects, EMDs, and TVDs) included maternal age, education (< 12, 12, 13–15, ≥ 16 years), tobacco use (smoker, nonsmoker), ethnicity (Hispanic, non-Hispanic white), and alcohol use (yes, no), as well as parity at time of pregnancy (0, 1, 2, > 2) and infant sex. Gestational age was also included in the analysis of term birth weight. Elevation of maternal residence also was considered in the analysis because most wells are < 7,000 feet, and elevation has been associated with both preterm birth and low birth weight (Niermeyer et al. 2009). For 272 births where elevation of maternal residence was missing, elevation was imputed using mean elevation for maternal ZIP code. For outcomes with very few events, only elevation was included in the multiple logistic modeling to avoid unstable estimates. The ORs and their 95% CIs were used to approximate relative risks for each outcome associated with IDW count exposure tertile (low, medium, and high) compared with no wells within 10 miles, which is reasonable because of the rarity of the outcomes. We considered the statistical significance of the association, as well as the trend, in evaluating results, at an alpha of 0.05. We evaluated the confounding potential of the 1998 introduction of folic acid fortification on the birth defect outcomes and found only a decrease in

NTD prevalence after 1998 (see Supplemental Material, Table S1).

In a sensitivity analyses, we explored reducing exposure to 2- and 5-mile buffers around the maternal residence, as well as restricting the cohort to births occurring between 2000 and 2009 to exclude births before the expansion of NGD. We report estimated associations with 95% CIs. All statistical analyses were conducted using SAS® software version 9.3 (SAS Institute Inc., Cary, NC).

Results

Births were approximately evenly divided between exposed and unexposed groups (0 wells in a 10-mile radius versus ≥ 1 well in a 10-mile radius) (Table 1). Estimated exposure, represented by IDW well counts, tended to be higher for births to mothers with residence addresses at lower elevations (< 6,000 feet), and among nonsmoking and Hispanic mothers (Table 1).

Both crude and adjusted estimates indicate a monotonic increase in the prevalence of CHDs with increasing exposure to NGD, as represented by IDW well counts (Table 2). Births to mothers in the most exposed tertile (> 125 wells/mile) had a 30% greater prevalence of CHDs (95% CI: 1.2, 1.5) than births to mothers with no wells within a 10-mile radius of their residence.

Prevalence of NTDs was positively associated with only the third exposure tertile, based on crude and estimated adjusted ORs for elevation (Table 2). Births in the highest tertile (> 125 wells/mile) were 2.0 (95% CI: 1.0, 3.9) times more likely to have a NTD than those with no wells within a 10-mile radius, based on 59 available cases. We observed no statistically significant associations between oral clefts and NGD, based on trend analysis across categorical IDW well count exposure (Table 2).

Both crude and adjusted estimates for preterm birth suggest a slight (< 10%) decreased risk of preterm birth with increasing exposure to NGD (Table 3). Crude term low birth weight measures suggested decreased risk of term low birth weight with increasing exposure to NGD. A weak nonlinear trend remained after adjusting for elevation and other covariates. This association is consistent with the multiple linear regression results for continuous term birth weight, in which mean birth weights were 5–24 g greater in the higher IDW well count exposure tertiles than the referent group.

We observed a monotonic increase in the prevalence of NTDs with increasing exposure to NGD in our sensitivity analyses using 2- and 5-mile exposure radii as well as some attenuation in decreased risk for preterm birth and term low birth weight (see Supplemental Material, Tables S2–7). Restricting births to 2000 through 2009, the period of most intense NGD in Colorado, attenuated the positive association between NTDs in the highest tertile and did not alter observed relationships for other birth outcomes (see Supplemental Material, Tables S2–S7).

Exploratory analysis of CHDs by clinical diagnostic groups indicates increased prevalence of PAV defects by 60% (95% CI: 1.1, 2.2), VSDs by 50% (95% CI: 1.1, 2.1), and TVDs by 400% (95% CI: 1.3, 13) in the most exposed tertile compared with those with no wells within a 10-mile radius (Table 4).

Discussion

We found positive associations between density and proximity of natural gas wells within a 10-mile radius of maternal residence and birth prevalence of CHDs and possibly NTDs. Prevalence of CHDs increased monotonically from the lowest to highest exposure tertile, although even in the highest tertile the magnitude of the association was modest. Prevalence of NTDs was elevated only in the highest tertile of exposure. We also observed small negative associations between density and proximity of natural gas wells within a 10-mile radius of maternal residence and

Table 1. Study population characteristics for unexposed and exposed subjects from rural Colorado 1996–2009.

Maternal or infant characteristic	Total	Referent group (0 wells within 10 miles)	Low (first tertile)[a]	Medium (second tertile)[a]	High (third tertile)[a]
Total *n* (%)	124,842	66,626 (53)	19,214 (15)	19,209 (15)	19,793 (16)
Median	27	27	26	27	27
25th percentile	22	22	21	22	23
75th percentile	32	32	30	31	31
Maternal ethnicity (%)[b]					
Non-Hispanic white	73	74	72	76	69
Sex (%)					
Male	51	51	51	51	51
Maternal smoking (%)[c]					
Smokers	11	11	14	13	8
Maternal alcohol (%)[c]					
No	99	98	99	99	99
Parity (%)					
0	33	33	31	32	32
1	23	23	24	24	25
2	19	19	20	19	20
> 2	25	25	26	25	24
Residential elevation (feet)					
Median	5,000–5,999	6,000–6,999	< 5,000	5,000–5,999	< 5,000
25th percentile	< 5,000	5,000–5,999	< 5,000	< 5,000	< 5,000
75th percentile	7,000–7,999	7,000–7,999	5,000–5,999	6,000–6,999	5,000–5,999
Maternal education (%)					
< 12 years	21	20	26	19	22
12 years	30	30	33	29	28
13–15 years	23	22	25	25	24
≥ 16 years	26	28	18	26	27

[a]First tertile, 1–3.62 wells/mile; second tertile, 3.63–125 wells/mile; third tertile, 126–1,400 wells/mile. [b]Includes both Non-Hispanic and Hispanic white. [c]During pregnancy.

Table 2. Association between inverse distance weighted well count within 10-mile radius of maternal residence and CHDs, NTDs, and oral clefts.

Inverse distance weighted well count[a]	0 wells within 10 miles	Low (first tertile)	Medium (second tertile)	High (third tertile)	Cochran–Armitage trend test *p*-value[b]
Live births (*n*)	66,626	19,214	19.209	19,793	
CHDs					
Cases (*n*)	887	281	300	355	
Crude OR	1	1.1	1.2	1.3	< 0.0001
Adjusted OR (95% CI)[c]		1.1 (0.93, 1.3)	1.2 (1.0, 1.3)	1.3 (1.2, 1.5)	
NTDs					
Cases (*n*)	27	6	7	19	
Crude OR	1	0.77	0.90	2.4	0.01
Adjusted OR (95% CI)[d]		0.65 (0.25, 1.7)	0.80 (0.34, 1.9)	2.0 (1.0, 3.9)	
Oral clefts					
Cases (*n*)	139	31	41	40	
Crude OR	1	0.77	1	0.97	0.9
Adjusted OR (95% CI)[c]		0.65 (0.43, 0.98)	0.89 (0.61, 1.3)	0.82 (0.55, 1.2)	

[a]First tertile, 1–3.62 wells/mile; second tertile, 3.63–125 wells/mile; third tertile, 126–1,400 wells/mile. [b]Performed as two-tailed test on unadjusted logistic regression. [c]Adjusted for maternal age, ethnicity, smoking, alcohol use, education, and elevation of residence, as well as infant parity and sex. [d]Adjusted only for residence elevation because of low numbers.

preterm birth and term low birth weight, and a small positive association with mean birth weight. We found no indication of an association between density and proximity of natural gas wells within a 10-mile radius of maternal residence and oral cleft prevalence.

Nongenetic risk factors for CHDs and NTDs possibly attributable to NGD include maternal exposure to benzene (Lupo et al. 2010b; Wennborg et al. 2005), PAHs (Ren et al. 2011), solvents (Brender et al. 2002; Chevrier et al. 1996; Desrosiers et al. 2012; McMartin et al. 1998), and air pollutants (NO_2, SO_2, PM) (Vrijheid et al. 2011). NGD emits multiple air pollutants, including benzene and toluene, during the "well completion" phase (when gas and water flow back to the surface after hydraulic fracturing) as well as from related infrastructure (CDPHE 2009a, 2009b; Garfield County Public Health Department 2009; Gilman et al. 2013; McKenzie et al. 2012; Pétron et al. 2012). Ambient benzene levels in areas with active NGD in Northeast Colorado ranged from 0.03 to 6 parts per billion by volume (ppbv) (CDPHE 2012; Gilman et al. 2013; Pétron et al. 2012). Furthermore, 24-hr average ambient air benzene levels near active well development sites in western Colorado ranged from 0.03 to 22 ppbv (McKenzie et al. 2012).

Two previous case–control studies have reported associations between maternal exposure to benzene and birth prevalence of NTDs and/or CHDs (Lupo et al. 2010b; Wennborg et al. 2005). The study by Lupo et al. (2010b) of 4,531 births in Texas found that mothers living in census tracts with the highest ambient benzene levels (0.9–2.33 ppbv) were 2.3 times more likely to have offspring with spina bifida than mothers living in census tracts with the lowest ambient benzene levels (95% CI: 1.22, 4.33). An occupational study of Swedish laboratory employees found a significant association between exposure to occupational levels of benzene in the critical window between conception, organogenesis, and neural crest formation and neural crest malformations (Wennborg et al. 2005). Children born to 298 mothers exposed to benzene had 5.3 times greater prevalence of neural crest malformations than children born to mothers not exposed to benzene (95% CI: 1.4, 21.1). Other studies of maternal exposures to organic solvents, some of which contain benzene, have reported associations between maternal occupational exposure to organic solvents and major birth defects (Brender et al. 2002; Desrosiers et al. 2012; McMartin et al. 1998). Although exposure to benzene is a plausible explanation for the observed associations, further research is needed to examine whether these associations are replicated and whether benzene specifically explains these associations.

Air pollutants emitted from diesel engines used extensively in NGD also may be associated with CHDs and/or NTDs. Trucks with diesel engines are used to transport supplies, water, and waste to and from gas wells, with 40 to 280 truck trips per day per well pad during development (Witter et al. 2013). Generators equipped with diesel engines are used in both drilling wells and hydraulic fracturing. Air pollutants in diesel exhaust include NO_2, SO_2, PM, and PAHs. A meta-analysis of four studies suggested associations of maternal NO_2 and SO_2 exposures with coarctation of the aorta and tetralogy of Fallot, and of maternal PM_{10} exposure with arterial septal defects (Vrijheid et al. 2011). Two case–control studies in China reported positive associations between PAH concentrations in maternal blood and the placenta and NTDs (Li et al. 2011; Naufal et al. 2010). Several CHDs were associated with traffic related carbon monoxide and ozone pollution in a case control study of births from 1987 to 1993 in Southern California (Ritz et al. 2002).

The small negative associations with term low birth weight and preterm birth in our study population were unexpected given that other studies have reported postive associations between these outcomes and urban air pollution (Ballester et al. 2010; Brauer et al. 2008; Dadvand et al. 2013; Ghosh et al. 2012; Llop et al. 2010) and proximity to natural gas wells (Hill 2013). It is possible that rural air quality near natural gas wells in Colorado is not as compromised as urban air quality in these studies, and exposure represented as IDW well count may not adequately

Table 3. Association between inverse distance weighted well count within 10-mile radius of maternal residence and preterm birth and term low birth weight.

Inverse distance weighted well count[a]	0 wells within 10 miles	Low (first tertile)	Medium (second tertile)	High (third tertile)	Cochran–Armitage trend test *p*-value[b]
Preterm birth					
Live births (*n*)	65,506	18,884	18,854	19,384	
Cases (*n*)	4,849	1,358	1,289	1,274	
Crude OR	1	0.97	0.92	0.88	< 0.0001
Adjusted OR (95% CI)[c]		0.96 (0.89, 1.0)	0.93 (0.87, 1.0)	0.91 (0.85, 0.98)	
Term low birth weight					
Full-term live births (*n*)	60,653	17,525	17,565	18,104	
Cases (*n*)	2,287	525	471	432	
Crude OR	1	0.79	0.70	0.62	< 0.0001
Adjusted OR (95% CI)[c]		1.0 (0.9, 1.1)	0.86 (0.77, 0.95)	0.9 (0.8, 1)	
Mean difference in birth weight (g)[d]	0	5 (–2.2, 13)	24 (17, 31)	22 (15, 29)	

[a]First tertile, 1–3.62 wells/mile; second tertile, 3.63–125 wells/mile; third tertile, 126–1,400 wells/mile. [b]Performed as two-tailed test on unadjusted logistic regression. [c]Adjusted for maternal age, ethnicity, smoking, alcohol use, education, and elevation of residence, as well as infant parity and sex. [d]Adjusted for maternal age, ethnicity, smoking, alcohol use, education, and elevation of residence, as well as infant parity, sex, and gestational age.

Table 4. Association between inverse distance weighted well count within 10-mile radius of maternal residence and CHD diagnostic groups.

Inverse distance weighted well count[a]	0 wells within 10 miles	Low (first tertile)	Medium (second tertile)	High (third tertile)
Conotruncal defects				
Cases (*n*)	40	14	13	15
Adjusted OR (95% CI)[b]	1	1.1 (0.57, 2.2)	1.1 (0.55, 2.0)	1.2 (0.6, 2.2)
Ventricular septal defects				
Cases (*n*)	210	68	59	84
Adjusted OR (95% CI)[c]	1	1.3 (0.96, 1.8)	1.1 (0.81, 1.5)	1.5 (1.1, 2.1)
Endocardial cushion and mitrovalve defects				
Cases (*n*)	39	14	12	12
Adjusted OR (95% CI)[b]		0.81 (0.42, 1.6)	0.80 (0.41, 1.5)	0.67 (0.33, 1.32)
Pulmonary artery and valve defects				
Cases (*n*)	137	52	62	66
Adjusted OR (95% CI)[c]	1	1.3 (0.89, 1.8)	1.5 (1.1, 2,1)	1.6 (1.1, 2,2)
Tricuspid valve defects				
Cases (*n*)	9	5	8	8
Adjusted OR (95% CI)[b]	1	2.6 (0.75, 9.1)	3.9 (1.3, 11)	4.2 (1.3, 13)
Aortic artery and valve defects				
Cases (*n*)	75	22	21	24
Adjusted OR (95% CI)[c]	1	1.1 (0.68, 1.9)	1.0 (0.62, 1.8)	1.2 (0.73, 2.1)
Patent ductus arteriosis				
Cases (*n*)	59	18	17	15
Adjusted OR (95% CI)[c]	1	1.0 (0.56, 1.8)	0.96 (0.55, 1.7)	0.83 (0.44, 1.5)

[a]First tertile, 1–3.62 wells/mile; second tertile, 3.63–125 wells/mile; third tertile, 126–1,400 wells/mile. [b]Adjusted only for residence elevation of because of low numbers. [c]Adjusted for maternal age, ethnicity, smoking, alcohol use, education, and elevation of residence, as well as infant parity and sex.

represent air quality. In addition, the power of our large cohort increases the likelihood of false positive results for small associations close to the null. Although associations were consistent across measures of birth weight (i.e., reduced risk of term low birth weight and increase in mean birth weight), they attenuated toward the null in sensitivity analysis for 2- and 5-mile radii (see Supplemental Material, Tables S6–S7). If causal, stronger associations would be expected with more stringent exposure definions. Our incomplete ability to adjust for socioeconomic status, health, nutrition, prenatal care, and pregnancy complications likely accounts for these unexpected findings.

This study has several limitations inherent in the nature of the available data. Not all birth defects were confirmed by medical record review. Also, birth defects are most likely undercounted, because stillbirths, terminated pregnancies, and later-life diagnoses (after 3 years of age) are not included. Birth weight and gestational age were obtained from birth certificates, which are generally accurate for birth weight and useful but less accurate for gestational age (DiGiuseppe et al. 2002). Data on covariates were obtained from birth certificates and were limited to basic demographic, education, and behavioral information available in the vital records. Distribution of covariates among exposure tertiles and the unexposed group was similar; nevertheless, our incomplete ability to adjust for socioeconomic status, health, nutrition, prenatal care, and pregnancy complications may have resulted in residual confounding. In addition, low event outcomes (e.g., NTDs) were adjusted only for elevation. The data set did not contain information on maternal folate consumption and genetic anomalies, both independent predictors of our outcomes, which may have confounded these results. We did observe a large decrease in the prevalence of NTDs after the introduction of folic acid in 1998, and small increases in the prevalence of CHDs and oral clefts, although none of the estimates are statistically significant (see Supplemental Material, Table S1). Further study is needed to determine whether unaccounted folate confounding is attenuating our results toward the null. There is no evidence indicating genetic anomalies would differ by IDW well count around maternal residence.

Because of the rarity of specific birth defects in the study population, birth defects were aggregated into three general groups. This limited our study in that associations with specific birth defects may have been obscured. An exploratory analysis of CHDs by clinical diagnostic groups indicates increased prevalence of specific diagnostic groups (i.e., PAV, VSD, and TVD) compared with aggregated CHDs (Table 4).

Another limitation of this study is the lack of temporal and spatial specificity of the exposure assessment. Because we did not have maternal residential history, we assumed that maternal address at time of delivery was the same as maternal address during the first trimester of pregnancy—the critical time period for formation of birth defects. Studies in Georgia and Texas estimate that 22–30% of mothers move residence during their pregnancy, and most mothers move within their locality (Lupo et al. 2010a; Miller et al. 2010), potentially introducing some exposure misclassification for the early pregnancy period of interest. However, these studies found little difference in mobility between cases and controls (Lupo et al. 2010a; Miller et al. 2010), and maternal mobility did not significantly influence the assessment of benzene exposure (Lupo et al. 2010a). We were able to determine only whether a well existed within the calendar year of birth (e.g., 2003) and did not have sufficient data to determine if a well existed within the first trimester of the pregnancy. Therefore, some nondifferential exposure misclassification is likely and the overall effect of this is unknown.

Similarly, we had consistent information only on existence of a well in the birth year. Lack of information on natural gas well activity levels, such as whether or not wells were producing or undergoing development, may have resulted in exposure misclassification. Actual exposure to natural gas–related pollutants likely varies by intensity of development activities. Lack of temporal and spatial specificity of the exposure assessment would most likely have tended to weaken associations (Ritz et al. 2007; Ritz and Wilhelm 2008). To address spatial and temporal variability, additional air pollution measurements and modeling will be needed to improve exposure estimates at specific locations. Last, information on the mother's activities away from her residence, such as work and recreation, as well as proximity of these activities to NGD was not available and may have led to further exposure misclassification and residual confounding.

Conclusion

This study suggests a positive association between greater density and proximity of natural gas wells within a 10-mile radius of maternal residence and greater prevalence of CHDs and possibly NTDs, but not oral clefts, preterm birth, or reduced fetal growth. Further studies incorporating information on specific activities and production levels near homes over the course of pregnancy would improve exposure assessments and provide more refined effect estimates. Recent data indicate that exposure to NGD activities is increasingly common. The COGCC estimates that 26% of the > 47,000 oil and gas wells in Colorado are located within 150–1,000 feet of a home or other type of building intended for human occupancy (COGCC 2012). Taken together, our results and current trends in NGD underscore the importance of conducting more comprehensive and rigorous research on the potential health effects of NGD.

References

Agency for Toxic Substances and Disease Registry. 2007. Toxicological Profile for Benzene. Available: http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=40&tid=14 [accessed 22 May 2013].

Ballester F, Estarlich M, Iniguez C, Llop S, Ramon R, Esplugues A, et al. 2010. Air pollution exposure during pregnancy and reduced birth size: a prospective birth cohort study in Valencia, Spain. Environ Health 9:6; doi:10.1186/1476-069X-9-6.

Bowen S, Irtenkauf S, Hannigna J, Stefanski A. 2009. Alterations in rat morphology following abuse patterns of toluene exposure. Reprod Toxicol 27:161–169.

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Sci Technol 116:680–686.

Brender JD, Suarez L, Hendricks KA, Baetz RA, Larsen R. 2002. Parental occupation and neural tube defect-affected pregnancies among Mexican Americans. J Occup Environ Med 44:650–656.

Brent RL. 2004. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. Pediatrics 113:957–968.

Bukowski JA. 2001. Review of the epidemiological evidence relating toluene to reproductive outcomes. Regul Toxicol and Pharmacol 33:147–156.

CDPHE (Colorado Department of Public Health and Environment). 2007. Garfield County Air Toxics Inhalation: Screening Level Human Health Risk Assessment: Inhalation Of Volatile Organic Compounds Measured In Rural, Urban, and Oil & Gas Areas In Air Monitoring Study (June 2005–May 2007). Available: http://www.garfield-county.com/public-health/documents/Working%20Draft%20CDPHE%20Screeing%20Level%20Risk%20Air%20Toxics%20Assessment%2012%2020%2007.pdf [accessed 22 May 2013].

CDPHE (Colorado Department of Public Health and Environment). 2009a. Garfield County Emissions Inventory. Available: http://www.garfield-county.com/air-quality/documents/airquality/Garfield_County_Emissions_Inventory-2009.pdf [accessed 22 May 2013].

CDPHE (Colorado Department of Public Health and Environment). 2009b. State of Colorado Technical Support Document for Recommended 8-Hour Ozone Designations. Available: http://www.colorado.gov/cs/Satellite?blobcol=urldata&blobheadername1=Content-Disposition&blobheadername2=Content-Type&blobheadervalue1=inline%3B+filename%3D%22Recommended+8-+Hour+Ozone+Area+Designations.pdf%22&blobheadervalue2=application%2Fpdf&blobkey=id&blobtable=MungoBlobs&blobwhere=1251808873080&ssbinary=true [accessed 22 May 2013].

CDPHE (Colorado Department of Public Health and Environment). 2012. Air Emissions Case Study Related to Oil and Gas Development in Erie, Colorado. Available: http://www.colorado.gov/airquality/tech_doc_repository.aspx [accessed 22 May 2013].

Centers for Disease Control and Prevention. 2013. Birth Defects. Available: http://www.cdc.gov/ncbddd/birthdefects/index.html [accessed 22 May 2013].

Chevrier C, Dananche B, Bahuau M, Nelva A, Herman C, Francannet C, et al. 1996. Occupational expsoure to organic solvent mixtures during pregancy and the the risk of non-syndromic oral clefts. Occup Environ Med 63:617–623.

COGCC (Colorado Oil and Gas Conservation Commission). 2009. Statement of Basis, Specific Statutory Authority, and Purpose: New Rules and Amendments to Current Rules of the Colorado Oil and Gas Conservation Commission, 2 ccr 404-1. Available: http://cogcc.state.co.us/ [accessed 22 May 2013].

COGCC (Colorado Oil and Gas Conservation Commission). 2012. Staff Report. Colorado Department of Natural Resources. Available: http://cogcc.state.co.us/ [accessed 22 May 2013].

COGIS (Colorado Oil and Gas Information System). 2011. Well Production Database. Vol. 2011. Available: http://cogcc.state.co.us/ [accessed 22 May 2013].

Colborn T, Kwiatkowski C, Schultz K, Bachran M. 2011. Natural gas operations from a public health perspective. Hum Ecol Risk Asses 17:1039–1056.

CRCSN (Colorado Responds to Children with Special Needs). 2011. Birth Defects Dataset Details. Available: http://www.cdphe.state.co.us/cohid/crcsndata.html [accessed 6 October 2011].

Dadvand P, Parker JD, Bell ML, Bonzini M, Brauer M, Darrow L, et al. 2013. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect 121:367–373; doi:10.1289/ehp.1205575.

Desrosiers TA, Lawson CC, Meyer RE, Richardson DB, Daniels JL, Waters MA, et al. 2012. Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts. Occup Environ Med 69:493–499.

DiGiuseppe DL, Aron DC, Ranbom L, Harper DL, Rosenthal GE. 2002. Reliability of birth certificate data: a multi-hospital comparison to medical records information. Matern Child Health J 6:169–179.

Esswein EJ, Breitenstein M, Snawder J, Kiefer M, Sieber K. 2013. Occupational exposure to respirable crystalline silica during hydraulic fracturing. J Occup Environ Hyg 10(7):347–356; doi:10.1080/15459624.2103.788352.

Frazier A. 2009. Analysis of Data Obtained for the Garfield County Air Toxics Study—Summer 2008. Available: http://www.garfield-county.com/air-quality/documents/airquality/2008_Targeted_Oil_and_Gas_Monitoring_Report.pdf [accessed 22 May 2013].

Garfield County Public Health Department. 2009. Garfield County 2009 Air Quality Monitoring Summary. Available: http://www.garfield-county.com/air-quality/documents/airquality/2009_Air_Monitoring_Report.pdf [accessed 22 May 2013].

Ghosh JKC, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett M, et al. 2012. Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics. Am J Epidemiol 175:1262–1274.

Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D, et al. 2005. Relation between ambient air quality and selected birth defects, Seven County Study, Texas, 1997–2000. Am J Epidemiol 162(3):238–252.

Gilman JB, Lerner BM, Kuster WC, de Gouw J. 2013. Source signature of volatile organic compounds (VOCs) from oil and natural gas operations in northeastern Colorado. Environ Sci Technol 47(3):1297–1305.

Hill EL. 2013. Unconventional Natural Gas Development and Infant Health: Evidence from Pennsylvania. Ithaca, NY:Charles Dyson School of Applied Economics and Management, Cornell University. Available: http://dyson.cornell.edu/research/researchpdf/wp/2012/Cornell-Dyson-wp1212.pdf [accessed 7 March 2014].

Honein M, Rasmussen S, Reefhuis J, Romitti P, Lammer E, Sun L, et al. 2006. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. Epidemiology 18:226–233.

Kemball-Cook S, Bar-Ilan A, Grant J, Parker L, Jung J, Santamaria W, et al. 2010. Ozone impacts of natural gas development in the Haynesville shale. Environ Sci Technol 44:9357–9363.

King GE. 2012. Hydraulic Fracturing 101: What Every Representative, Environmentalist, Regulator, Reporter, Investor, University Researcher, Neighbor and Engineer Should Know About Estimating Frac Risk and Improving Frac Performance in Unconventional Gas and Oil Wells. Available: http://fracfocus.org/sites/default/files/publications/hydraulic_fracturing_101.pdf [accessed 6 March 2014].

Li Z, Zhang L, Ye R, Pei L, Liu J, Zheng X, et al. 2011. Indoor air pollution from coal combustion and the risk of neural tube defects in a rural population in Shanxi Province, China. Am J Epidemiol 174:451–458.

Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iñiguez C. 2010. Preterm birth and exposure to air pollutants during pregnancy. Environ Res 110:778–785.

Lupo PJ, Symanski E, Chan W, Mitchell LE, Waller DK, Canfield MA, et al. 2010a. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. Paediatr Perinat Epidemiol 24:200–208.

Lupo P, Symanski E, Waller D, Chan W, Langlosi P, Canfield M, et al. 2010b. Maternal exposure to ambient levels of benzene and neural tube defects among offspring, Texas 1999–2004. Environ Health Perspect 119:397–402; doi:10.1289/ehp.1002212.

McKenna MT, Michaud CM, Murray CJL, Marks JS. 2005. Assessing the burden of disease in the United States using disability-adjusted life years. Am J Prev Med 28:415–423.

McKenzie LM, Witter RZ, Newman LS, Adgate JL. 2012. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ 424:79–87.

McMartin KI, Chu M, Kopecky E, Einarson TR, Koren G. 1998. Pregnancy outcome following maternal organic solvent exposure: a meta-analysis of epidemiologic studies. Amn J Ind Med 34:288–292.

Miller A, Siffel C, Correa A. 2010. Residential mobility during pregnancy: patterns and correlates. Matern Child Heatlh J 14:625–634.

National Center for Health Statistics. 2011. Classification of Diseases and Injuries. Available: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD-9/ucod.txt [accessed 22 May 2013].

Naufal Z, Zhiwen L, Zhu L, Zhou GOD, McDonald T, He LY, et al. 2010. Biomarkers of exposure to combustion by-products in a human population in Shanxi, China. J Expos Sci Environ Epidemiol 20:310–319.

Niermeyer S, Andrade Mollinedo P, Huicho L. 2009. Child health and living at high altitude. Arch Dis Child 94:806–811.

Olaguer EP. 2012. The potential near-source ozone impacts of upstream oil and gas industry emissions. J Air Waste Manag Assoc 62:966–977.

Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, et al. 2010. Updated national birth prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Res A Clin Mol Teratol 88:1008–1016.

Pétron G, Frost G, Miller BR, Hirsch AI, Montzka SA, Karion A, et al. 2012. Hydrocarbon emissions characterization in the Colorado front range: a pilot study. J Geophys Res 117:D04304; doi:10.1029/2011JD016360.

Ren A, Qiu X, Jin L, Ma J, Li Z, Zhang L, et al. 2011. Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects. Proc Natl Acad Sci USA 108:12770–12775.

Ritz B, Wilhelm M. 2008. Ambient air pollution and adverse birth outcomes: Methodologic issues in an emerging field. Basic Clinl Pharmacol Toxicol 102:182–190.

Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. 2007. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J of Epidemiol 166:1045–1052.

Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. 2002. Ambient air pollution and risk of birth defects in southern California. Am J Epidemiol 155:17–25.

Romitti P, Sun L, Honein M, Reefhuis J, Correa A, Rasmussen S. 2007. Maternal periconceptual alcohol consumption and risk of orofacial clefts. Am J Epidemiol 166:775–785.

Shepard T. 1995. Agents that cause birth defects. Yonsei Med J 36:393–396.

U.S. EIA (U.S. Energy Information System). 2011a. International Energy Outlook 2011. DOE/EIA-0484(2011). Washington, DC:U.S. EIA.

U.S. EIA (U.S. Energy Information System). 2011b. Review of Emerging Resources: U.S. Shale Gas and Shale Oil Plays. Available: http://www.eia.gov/analysis/studies/usshalegas/pdf/usshaleplays.pdf [accessed 22 May 2013].

Vidas H, Hugman B. 2008. Availability, Economics, and Production Potential of North American Unconventional Natural Gas Supplies. Available: http://www.ingaa.org/File.aspx?id=7878 [accessed 22 May 2013].

Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, et al. 2011. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect 119:598–606; doi:10.1289/ehp.1002946.

Wald N, Sneddon J. 1991. Prevention of neural tube defects: Results of the medical research council vitamin study. Lancet 338:131.

Walther E. 2011. Screening Health Risk Assessment Sublette County, Wyoming. SR2011-01-03. Available: http://www.sublettewyo.com/DocumentCenter/Home/View/438 [accessed 22 May 2013].

Wennborg H, Magnusson L, Bonde J, Olsen J. 2005. Congenital malformations related to maternal exposure to specific agents in biomedical research laboratories. J Occup Environ Med 47:11–19.

Witter R, McKenzie L, Stinson K, Scott K, Newman L, Adgate J. 2013. The use of health impact assessment for a community undergoing natural gas development. Am J Public Health 103 (6): doi: 10.2105/AJPH.2012.301017.

Zielinska B, Fujita E, Campbell D. 2011. Monitoring of Emissions from Barnett Shale Natural Gas Production Facilities for Population Exposure Assessment. Desert Research Institute. Available: https://sph.uth.edu/mleland/attachments/Barnett%20Shale%20Study%20Final%20Report.pdf [accessed 22 May 2013].

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307732.

Proximity to Natural Gas Wells and Reported Health Status: Results of a Household Survey in Washington County, Pennsylvania

Peter M. Rabinowitz,[1,2] Ilya B. Slizovskiy,[1,3] Vanessa Lamers,[3,4] Sally J. Trufan,[1,2] Theodore R. Holford,[3] James D. Dziura,[3] Peter N. Peduzzi,[3] Michael J. Kane,[3] John S. Reif,[5] Theresa R. Weiss,[1] and Meredith H. Stowe[1]

[1]Yale University School of Medicine, Yale University, New Haven, Connecticut, USA; [2]University of Washington, Seattle, Washington, USA; [3]Yale School of Public Health, and [4]Yale School of Forestry & Environmental Sciences, Yale University, New Haven, Connecticut, USA; [5]Colorado State University College of Veterinary Medicine & Biomedical Sciences, Colorado State University, Fort Collins, Colorado, USA

Background: Little is known about the environmental and public health impact of unconventional natural gas extraction activities, including hydraulic fracturing, that occur near residential areas.

Objectives: Our aim was to assess the relationship between household proximity to natural gas wells and reported health symptoms.

Methods: We conducted a hypothesis-generating health symptom survey of 492 persons in 180 randomly selected households with ground-fed wells in an area of active natural gas drilling. Gas well proximity for each household was compared with the prevalence and frequency of reported dermal, respiratory, gastrointestinal, cardiovascular, and neurological symptoms.

Results: The number of reported health symptoms per person was higher among residents living < 1 km (mean ± SD, 3.27 ± 3.72) compared with > 2 km from the nearest gas well (mean ± SD, 1.60 ± 2.14; $p = 0.0002$). In a model that adjusted for age, sex, household education, smoking, awareness of environmental risk, work type, and animals in house, reported skin conditions were more common in households < 1 km compared with > 2 km from the nearest gas well (odds ratio = 4.1; 95% CI: 1.4, 12.3; $p = 0.01$). Upper respiratory symptoms were also more frequently reported in persons living in households < 1 km from gas wells (39%) compared with households 1–2 km or > 2 km from the nearest well (31 and 18%, respectively) ($p = 0.004$). No equivalent correlation was found between well proximity and other reported groups of respiratory, neurological, cardiovascular, or gastrointestinal conditions.

Conclusion: Although these results should be viewed as hypothesis generating, and the population studied was limited to households with a ground-fed water supply, proximity of natural gas wells may be associated with the prevalence of health symptoms including dermal and respiratory conditions in residents living near natural gas extraction activities. Further study of these associations, including the role of specific air and water exposures, is warranted.

Citation: Rabinowitz PM, Slizovskiy IB, Lamers V, Trufan SJ, Holford TR, Dziura JD, Peduzzi PN, Kane MJ, Reif JS, Weiss TR, Stowe MH. 2015. Proximity to natural gas wells and reported health status: results of a household survey in Washington County, Pennsylvania. Environ Health Perspect 123:21–26; http://dx.doi.org/10.1289/ehp.1307732

Introduction

Unconventional methods of natural gas extraction, including directional drilling and hydraulic fracturing (also known as "fracking"), have made it possible to reach natural gas reserves in shale deposits thousands of feet underground (Myers 2012). Increased drilling activity in a number of locations in the United States has led to growing concern that natural gas extraction activities could contaminate water supplies and ambient air, resulting in unforeseen adverse public health effects (Goldstein et al. 2012). At the same time, there is little peer-reviewed evidence regarding the public health risks of natural gas drilling activities (Kovats et al. 2014; McDermott-Levy and Kaktins 2012; Mitka 2012), including a lack of systematic surveys of human health effects.

The process of natural gas extraction. Natural gas extraction of shale gas reserves may involve multiple activities occurring over a period of months. These include drilling and casing of deep wells that contain both vertical and horizontal components as well as placement of underground explosives and transport and injection of millions of gallons of water containing sand and a number of chemical additives into the wells at high pressures to extract gas from the shale deposits (hydraulic fracturing) (Jackson RE et al. 2013). Chemicals used in the hydraulic fracturing process can include inorganic acids, polymers, petroleum distillates, anti-scaling compounds, microbicides, and surfactants (Vidic et al. 2013). Although some of these fluids are recovered during the fracking process as "flowback" or "produced" water, a significant amount (as much as 90%) (Vidic et al. 2013) may remain underground. The recovered flowback water—which may contain chemicals added to the fracking fluid as well as naturally occurring chemicals such as salts, arsenic, and barium and naturally occurring radioactive material originating in the geological formations—may be stored in holding ponds or transported offsite for disposal and/or wastewater treatment elsewhere.

Potential water exposures. Although much of the hydraulic fracturing process takes place deep underground, there are a number of potential mechanisms for chemicals used in the fracturing process as well as naturally occurring minerals, petroleum compounds (including volatile organic compounds; VOCs), and other substances of flowback water (Chapman et al. 2012) to enter drinking-water supplies. These include spills during transport of chemicals and flowback water, leaks of a well casing (Kovats et al. 2014), leaks through underground fissures in rock formations, runoff from drilling sites, and disposal of fracking flowback water (Rozell and Reaven 2012). Studies have reported increased levels of methane in drinking water wells located < 1 km from natural gas drilling, suggesting contamination of water wells from hydraulic

Address correspondence to P.M. Rabinowitz, University of Washington School of Public Health, Department of Environmental and Occupational Health, 1959 NE Pacific St., F551 Health Sciences Center, Box 357234, Seattle, WA 98195 USA. Telephone: (206) 685-2654. E-mail: peterr7@uw.edu

Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1307732).

We thank the Southwest Pennsylvania Environmental Health Project for assistance with pretesting of the community survey, L. Conti for assistance with study design, D. Galusha and F. Li for assistance with data analysis, and J. Bonthius for assistance with data entry and management.

This study was supported by grants from The Heinz Endowments, as well as the 11th Hour Project, a program of the Schmidt Family Foundation, and the Claneil Foundation. Additional support was received from the Jan Stolwijk Fellowship fund and by the Yale University Clinical and Translational Science Award grant UL1 RR024139 from the National Center for Research Resources and the National Center for Advancing Translational Science, components of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research. None of the funders participated in the study design, data collection, or analysis of study results.

P.M.R. and J.D.D. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH.

The authors declare they have no actual or potential competing financial interests.

Received: 17 October 2013; Accepted: 20 August 2014; Advance Publication: 10 September 2014; Final Publication: 1 January 2015.

fracturing activities (Jackson RB et al. 2013; Osborn et al. 2011), although natural movement of methane and brine from shale deposits into aquifers has also been suggested (Warner et al. 2012). If contaminants from hydraulic fracturing activities were able to enter drinking water supplies or surface water bodies, humans could be exposed to such contaminants through drinking, cooking, showering, and swimming.

Potential air exposures. The drilling and completion of natural gas wells, as well as the storage of waste fluids in containment ponds, may release chemicals into the atmosphere through evaporation and off-gassing. In Pennsylvania, flowback fluids are not usually disposed of in deep injection wells; therefore surface ponds containing flowback fluids are relatively common and could be sources of air contamination through evaporation. Flaring of gas wells, operation of diesel equipment and vehicles, and other point sources for air quality contamination around drilling activities may also pose a risk of respiratory exposures to nitrogen oxides, VOCs, and particulate matter. Release of ozone precursors into the environment by natural gas production activities may lead to increases in local ozone levels (Olaguer 2012). Well completion and gas transport may cause leakage of methane and other greenhouse gases into the environment (Allen 2014). Studies in Colorado have reported elevated air levels of VOCs including trimethylbenzenes, xylenes, and aliphatic hydrocarbons related to well drilling activities (McKenzie et al. 2012).

Human health impact. Concerns about the impact of natural gas extraction on the health of nearby communities have included exposures to contaminants in water and air described above as well as noise and social disruption (Witter et al. 2013). A published case series cited the occurrence of respiratory, skin, neurological, and gastrointestinal symptoms in humans living near gas wells (Bamberger and Oswald 2012). A convenience sample survey of 108 individuals in 55 households across 14 counties in Pennsylvania who were concerned about health effects from natural gas facilities found that a number of self-reported symptoms were more common in individuals living near gas facilities, including throat and nasal irritation, eye burning, sinus problems, headaches, skin problems, loss of smell, cough, nosebleeds, and painful joints (Steinzor et al. 2013). Similarly, a convenience sample survey of 53 community members living near Marcellus Shale development found that respondents attributed a number of health impacts and stressors to the development. Stress was the symptom reported most frequently (Ferrar et al. 2013).

Here we report on the analysis of a cross-sectional, random-sample survey of the health of residents who had ground-fed water wells in the vicinity of natural gas extraction wells to determine whether proximity to gas wells was associated with reported respiratory, dermal, neurological, or gastrointestinal symptoms.

Methods

Selection of study area. The Marcellus formation, a principal source of shale-based natural gas in the United States, is a Middle Devonian–age black, low-density, organically rich shale that has been predominantly horizontally drilled for gas extraction in the southwestern portion of Pennsylvania since 2003 [Pennsylvania Spatial Data Access (PASDA) 2013]. In this study we focused on Washington County in southwestern Pennsylvania, an area of active natural gas drilling (Carter et al. 2011). At the time of the administration of the household survey during summer 2012, there were, according to the Pennsylvania Department of Environmental Protection, 624 active natural gas wells in Washington County. Of these natural gas wells, 95% were horizontally drilled (Pennsylvania Department of Environmental Protection 2012). The county has a highly rural classification with nearly 40% of the land devoted to agriculture (U.S. Department of Agriculture 2007). Washington County has a population of approximately 200,000 persons with 94% self-identified as white, 90% having at least a high school diploma, and a 2012 median household income of $53,545 (Center for Rural Pennsylvania 2014). We selected a contiguous set of 38 rural townships within the center of Washington County as our study site in order to avoid urban areas bordering Pittsburgh, which would be unlikely to have ground-fed water wells, and areas near the Pennsylvania border, which might be influenced by gas wells in other states (Figure 1).

Survey instrument. We designed a community environmental health assessment of reported health symptoms and health status based on questions drawn from publicly available surveys. Symptom questions, covering a range of organ systems that had been mentioned in published reports (Bamberger and Oswald 2012; Steinzor et al. 2013), asked respondents whether they or any household members had experienced each condition during the past year (see Supplemental Material, "Questionnaire"). The health assessment also asked a number

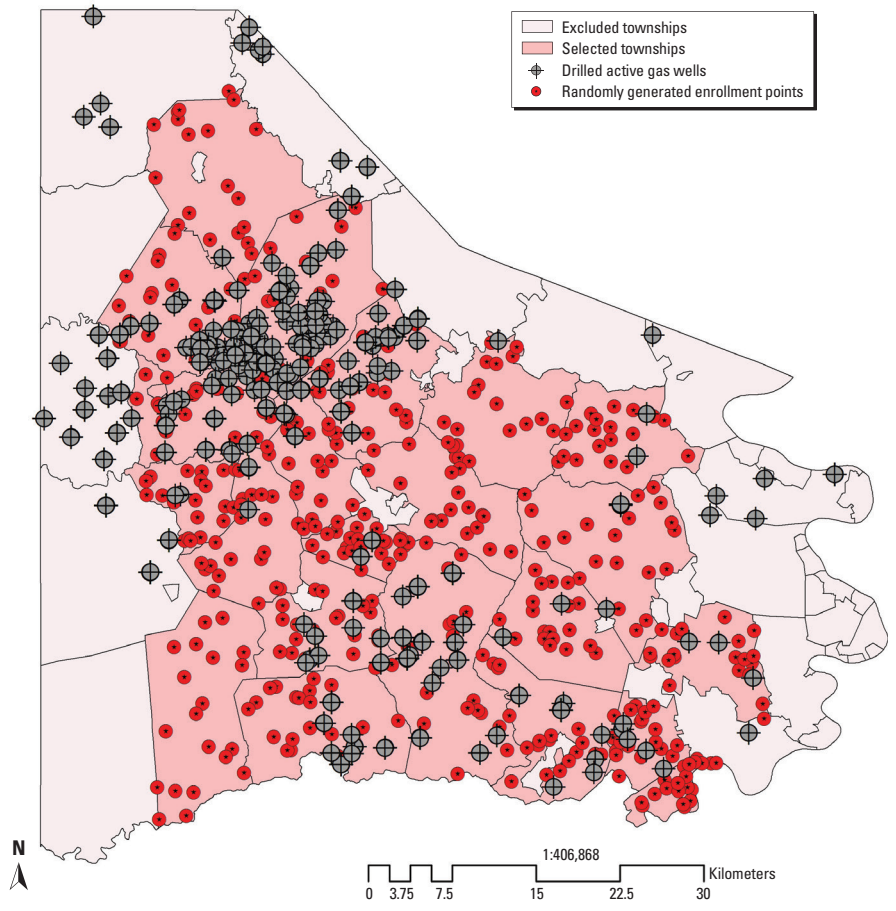


Figure 1. Distribution of drilled active Marcellus Shale natural gas wells ($n = 624$) and randomly generated sampling sites ($n = 760$) for eligible municipalities of Washington County, Pennsylvania.

of general yes/no questions about concerns of environmental hazards in the community, such as whether respondents were satisfied with air quality, water quality, soil quality, environmental noise and odors, and traffic, but did not specifically mention natural gas wells or hydraulic fracturing or other natural gas extraction activities. The survey was pretested with focus groups in the study area in collaboration with a community based group and revised to ensure comprehensibility of questions.

Selection and recruitment of households. Using ArcGIS Desktop 10.0 software (ESRI, Inc., Redlands, CA), we randomly selected 20 geographic points from each of 38 contiguous townships in the study county (Figure 1). We identified an eligible home nearest to each randomly generated sampling point, and visited each home to determine which households were occupied and had ground-fed water wells. We selected households with ground-fed water wells to assess possible health effects related to water contamination. From the original 760 points identified (i.e., 20 points in each of the 38 townships), we excluded 12 duplicate points and 64 points found not to correspond to a house structure (see Supplemental Material, Figure S1). After site visits by the study team who spoke to residents or neighbors, we excluded house locations determined not to have a ground-fed well or spring. Additional points were excluded if the structure was not occupied (n = 5) or inaccessible from the road (n = 4). During visits to eligible households, a study member invited a responding adult at least 18 years of age to participate in the survey, described as a survey of community environmental health that considered a number of environmental health factors. Three households were excluded when the respondent was unable to answer the questionnaire due to language or health problems. Eligible households were offered a small cash stipend for participation.

The Yale University School of Medicine Human Research Protection Program determined the study to be exempt from Human Subjects review. Respondents provided oral consent but were not asked to sign consent forms; their names were not recorded.

Of the 255 eligible households, respondents refused to complete the survey in 47 households, and we were not able to contact residents in another 26 households. Reasons for refusal included "not interested" (n = 8), "no time/too busy" (n = 3), "afraid" (n = 1), and 35 gave no reason. The rate of refusal varied by distance category, with 12 of 74 (16%) of households < 1 km from a gas well, 10 of 67 (15%) of households 1–2 km from wells, and 25 of 86 (25%) of eligible households > 2 km from a gas well refusing to participate, but the differences were not statistically significant. At the consenting 180 households (71% of eligible households), an adult respondent completed the survey covering the health status of the 492 individuals living in these households.

Administration of survey at residence. Trained study personnel administered the survey in English. The responding adult at the participating household reported on the health status of all persons in the household over the past year. A study team member recorded the global positioning system (GPS) coordinates of the household using a Garmin GPSMAP® 62S Series handheld GPS device (Garmin International, Inc., Olathe, KS). Survey personnel were not aware of the mapping results for gas well proximity to the households being surveyed.

Household proximity to nearest active gas well and age of wells. A map of 624 active natural gas wells in the study area, and their age and type, was created by utilizing gas well permit data publicly available at the PASDA (2013). Ninety five percent of the gas wells had "spud dates" (first date of drilling) between 2008 and 2012, with more than half of spud dates occurring in 2010 and 2011. We used ArcGIS to calculate the distance between each household location (as defined by the GPS reading taken during the site visit) and each natural gas well in the study area. We then classified households according to their distance from the nearest gas well with distance categories of < 1 km, 1–2 km, or > 2 km. We used 1 km as the initial cut point for distance to a nearest gas well because of the reported association of higher methane levels in drinking-water wells located < 1 km from natural gas wells (Osborn et al. 2011), and 2 km as the second cut point because it was close to the mean of the distances between households and nearest gas wells. The mean and median distance between a household and the nearest natural gas well were 2.0 km and 1.4 km, respectively. We classified the age of each gas well as the time interval between spud date and the date that the household survey was conducted during summer, 2012.

Statistical analysis. Demographic variables were analyzed for differences among individuals between distance categories using chi-square, analysis of variance, or generalized linear mixed-model statistics as appropriate. Reported occupation was classified as either blue collar, office sales and service, management/professional, or not working, using classifications of the U.S. Bureau of Labor Statistics (2014).

The prevalence of each outcome and the number of symptoms reported for each household member included in the study were calculated according to the distance of each household (< 1, 1–2, or > 2 km) from the nearest gas well. To test the association between household distance from a well and the overall number of symptoms as well as the presence or absence of each of six groups of health conditions (dermal, upper respiratory, lower respiratory, gastrointestinal, neurological, and cardiovascular), we used SAS 9.3 in a generalized linear mixed model (GLMM) analysis (SAS Institute Inc., Cary, NC). The analysis used maximum likelihood estimation with adaptive quadrature methods (Schabenberger 2007) including a random effect for household to account for the clustering of individuals within a household. The model was adjusted for age of individual (continuous), sex (binary), average adult household education (continuous), smoker present in household (yes/no), awareness of environmental hazard nearby (yes/no), employment type (four categories), and whether animals were present in the home or backyard (yes/no). Given the exploratory nature of this study, no adjustments were made for multiple comparisons and significance was established at the two-sided 0.05 level. Statistical analyses were conducted using SAS 9.3.

Results

Demographics. Individuals living in households < 1 km from gas wells were older (mean, 46.9 ± 21.9) compared with individuals in households > 2 km from a gas well (mean, 40.0 ± 23.5 years, p = 0.03) (Table 1). There was a higher proportion of children in the households > 2 km from a gas well compared with those < 1 km from a gas well (27% vs. 14%, p = 0.008). Families had lived in their homes an average of 22.8 ± 17.2 years at the time of the interview. Thirty-four percent of individuals had blue-collar jobs and 38% of the subjects were nonworkers (e.g., unemployed, students). Sixty-six percent reported using their ground-fed water (well or natural spring) for drinking water, and 84% reported using it for other activities such as bathing. The age of the nearest gas well was significantly greater for households < 1 km from a gas well (mean, 2.3 ± 1.6) compared with those 1–2 km or > 2 km from a well (1.5 ± 1.3 and 1.1 ± 0.9, respectively, p < 0.05). Reported smoking was less common in households near gas wells, whereas reported respondent awareness regarding environmental health risks was higher, although these differences were not statistically significant.

Reported health symptoms. The average number of reported symptoms per person in residents of households < 1 km from a gas well (3.27 ± 3.72) was greater compared with those living > 2 km from gas wells (1.60 ± 2.14, p = 0.0002).

Individuals living in households < 1 km from natural gas wells were more likely to

report having any of the queried skin conditions over the past year (13%) than residents of households > 2 km from a well (3%; χ^2 = 13.8, p = 0.001) (Table 2). Reported upper respiratory symptoms were also more frequent among households < 1 km (39%) compared with households > 2 km from gas wells (18%; χ^2 = 17.9, p = 0.0001).

In a hierarchical model that adjusted for age, sex, household education level, smokers in household, job type, animals in household, and awareness of environmental risk (Table 3), household proximity to natural gas wells remained associated with number of symptoms reported per person < 1 km (p = 0.002) and 1–2 km (p = 0.05) compared with > 2 km from gas wells, respectively. In similar models, living in a household < 1 km from the nearest gas well remained associated with increased reporting of skin conditions [odds ratio (OR) = 4.13; 95% confidence interval (CI): 1.38, 12.3] and upper respiratory symptoms (OR = 3.10; 95% CI: 1.45, 6.65) compared with households > 2 km from the nearest gas well.

For the other grouped symptom complexes examined, there was not a significant relationship in our adjusted model between the prevalence of symptom reports and proximity to nearest gas well. In the multivariate model, however, environmental risk awareness was significantly associated with report of all groups of symptoms.

Age of the nearest gas well was found to be negatively correlated with distance (r = –0.325; p < 0.0001): Gas wells < 1 km from households tended to be older than the nearest wells in other distance categories. When age of wells was added to the multivariate model, proximity to gas wells remained significantly associated with respiratory symptoms, but the association between proximity and dermal symptoms lost statistical significance.

Discussion

This spatially random health survey of households with ground-fed water supply in a region with a large number of active natural gas wells is to our knowledge the largest study to date of the association of reported symptoms and natural gas drilling activities. We found an increased frequency of reported symptoms over the past year in households in closer proximity to active gas wells compared with households farther from gas wells. This association was also seen for certain categories of symptoms, including skin conditions and upper respiratory symptoms. This association persisted even after adjusting for age, sex, smokers in household, presence of animals in the household, education level, work type, and awareness of environmental risks. Other groups of reported symptoms, including cardiac, neurological, or gastrointestinal symptoms, did not show a similar association with gas well proximity. These results support the need for further investigation of whether natural gas extraction activities are associated with community health impacts.

These findings are consistent with earlier reports of respiratory and dermal conditions in persons living near natural gas wells (Bamberger and Oswald 2012; Steinzor et al. 2013). Strengths of the study included the larger sample size compared with previously published surveys, and the random method of selecting households using geographic information system methodology, which reduces the possibility of selection bias (although only a subset of households, those with ground-fed water supply, were sampled).

A limitation of the study was the reliance on self-report of health symptoms. On one hand, symptoms in other household members may have been underreported by the household respondent; on the other hand, awareness bias in individuals concerned about the presence of an environmental health hazard would be more likely to increase reporting of illness symptoms, leading to recall bias of the results. We did not collect data on whether individuals were receiving financial compensation for gas well drilling on their property, which could have affected their willingness to report symptoms. It is possible that differential refusal to participate could have introduced potential for selection bias; for example, individuals who were receiving compensation for gas drilling on their property might be less willing to participate in the survey. We found instead that the refusal rate, though < 25% overall, was higher among households farther from gas wells, suggesting that such households may have been less interested in participating because they had less awareness of hazards. The study questionnaire did not include questions about natural gas extraction activities, in order to reduce awareness bias. At the same time, it is likely that household residents were aware of gas drilling activities in the vicinity of households; and the fact that reported environmental awareness by respondents was associated with the prevalence of all groups of reported health symptoms suggests a correlation between heightened awareness of health risks and reported health conditions. Nevertheless, the observed association between gas well proximity and reported dermal and upper respiratory symptoms persisted in the multivariate model even after adjusting for environmental awareness. Future studies should attempt to medically confirm particular diagnoses and further assess and control for the effect of awareness on reported health status.

Table 1. Demographics and household characteristics by proximity to the nearest natural gas well.

Characteristic	< 1 km	1–2 km	> 2 km	All
Individuals				
n	150	150	192	492
Sex				
Male	80 (53)	78 (52)	92 (48)	250 (51)
Female	70 (47)	72 (48)	100 (52)	242 (49)
Children	21 (14)*	27 (18)	52 (27)	100 (20)
Education (years)	13.4 ± 2.0	13.5 ± 1.9	13.3 ± 2.0	13.4 ± 1.9
Age (years)	46.9 ± 21.9**	45.5 ± 22.7	40.0 ± 23.5	43.8 ± 23.0
Occupation[a]				
M/P	29 (19)	34 (23)	33 (17)	96 (19)
O/S	17 (11)	11 (7)	14 (7)	42 (9)
BC	60 (40)	51 (34)	56 (29)	167 (34)
NW	44 (29)	54 (36)	89 (46)	187 (38)
Households				
n	62	57	61	180
Smoking[b]	7 (11)	12 (21)	14 (23)	33 (18)
Years in household (*n*)	23.7 ± 16.6	23.5 ± 16.4	21.2 ± 18.6	22.8 ± 17.2
Body mass index (kg/m^2)	27.9 ± 5.1	27.5 ± 5.4	27.9 ± 6.1	27.8 ± 5.5
Use ground-fed water				
Drinking	39 (63)	41 (72)	38 (62)	118 (66)
Other	54 (87)	51 (89)	46 (75)	151 (84)
Water has unnatural appearance	13 (21)	7 (12)	6 (10)	26 (14)
Taste/odor prevents water use	14 (23)	10 (18)	19 (31)	43 (24)
Dissatisfied with odor in environment	7 (11)	1 (2)	1 (2)	9 (5)
Environmental risk awareness[c]	16 (25)	16 (28)	9 (15)	41 (23)
Years since spud date of closest well (years)	2.3 ± 1.6#	1.5 ± 1.3	1.1 ± 0.9	1.6 ± 1.4

Values are *n* (%) or mean ± SD.

[a]Participant occupation was categorized into six main industries according to the U.S. Bureau of Labor Statistics (2014), and presented here in four main groups: M/P, management or professional; O/S, office, sales, or service; BC, blue collar (fishing, farming, and forestry; construction, extraction, maintenance, production, transportation, and material moving); NW, nonworker (student, disabled, retired, or unemployed). [b]Household smoking was determined when respondents were asked if they or at least one member of their household smoked cigarettes in the house at the time of the survey. [c]Household respondents were asked if they were aware of any environmental health risks near their residence (yes/no), to approximate potential sources of expectation or awareness bias. *p = 0.008 compared with > 2 km households. **p = 0.03 compared with > 2 km households. #p < 0.05 compared with 1–2 km and > 2 km households.

A further study limitation was the fact that our analysis includes multiple comparisons between groups of households, and the consequent possibility that random error could account for some of our findings. We limited such comparisons by grouping individual symptoms into organ system clusters. However, we acknowledge that the multiple comparisons used in the methodology mean that any such particular findings should be viewed as preliminary and hypothesis generating.

Our use of gas well proximity as a measure of exposure was an indirect measure of potential water or airborne exposures. More precise data could come from direct monitoring and modeling of air and water contaminants, and correlating such measured exposures with confirmed health effects should be a focus of future study. Biomonitoring of individuals living near natural gas wells could provide additional information about the role and extent of particular chemical exposures.

There are several potential explanations for the finding of increased skin conditions among inhabitants living near gas wells. One is that natural gas extraction wells could have caused contamination of well water through breaks in the gas well casing or other underground communication between ground water supplies and fracking activities. The geographic area studied has experienced petroleum and coal exploration and extraction activities in the past century, and such activities may increase the risk of chemicals in fracking fluid or flowback water entering ground water and contaminating wells. If such contamination did occur, several types of chemicals in fracking fluid have irritant properties and could potentially cause skin rashes or burning sensation through exposure during showers or baths. There are published reports of associations between the prevalence of eczema and other skin conditions with exposure to drinking water polluted with chemicals including VOCs (Chaumont et al. 2012; Lampi et al. 2000; Yorifuji et al. 2012) as well as changes in water hardness (Chaumont et al. 2012; McNally et al. 1998).

A second possible explanation for the skin symptoms could be exposure to air pollutants including VOCs, particulates, and ozone from upwind sources, such as flaring of gas wells (McKenzie et al. 2012) and exhaust from vehicles and heavy machinery.

A third possibility to explain the clustering of skin and other symptoms would be that they could be related to stress or anxiety that was greater for households living near gas wells. In this study, awareness of environmental risk was independently associated with overall reporting of symptoms as well as reporting of skin problems. However, in multivariate models, proximity to gas wells remained a significant predictor of symptoms even when adjusting for such awareness. These results argue for possible air or water contaminant exposures, in addition to stress, contributing to the observed patterns of increased health symptoms in households near gas wells. A fourth possibility would be the role of allergens or irritant chemicals not related to natural gas drilling activities, such as exposure to agricultural chemicals or household animals. We did not see a correlation between skin conditions and either the presence of an animal in the household or agricultural occupation, making this association less likely. At the same time, it is possible that other confounding could be present but not accounted for in our models.

Table 2. Prevalence of selected health conditions reported by individuals by proximity to the nearest gas well (2011–2012).[a]

Symptoms	< 1 km (*n* = 150)	1–2 km (*n* = 150)	> 2 km (*n* = 192)
Total number of symptoms per individual	3.27 ± 3.72	2.56 ± 3.26	1.60 ± 2.14
Dermal [*n* (%)]	19 (13)	7 (5)	6 (3)
Rashes/skin problems	10 (7)	7 (5)	6 (3)
Dermatitis	6 (4)	5 (3)	2 (1)
Irritation	6 (4)	2 (1)	1 (1)
Burning	8 (5)	4 (3)	1 (1)
Itching	9 (6)	5 (3)	2 (1)
Hair loss	2 (1)	0 (0)	1 (1)
Upper respiratory [*n* (%)]	58 (39)	46 (31)	35 (18)
Allergies/sinus problems	35 (23)	27 (18)	27 (14)
Cough/sore throat	10 (7)	3 (2)	2 (1)
Itchy eyes	19 (13)	22 (15)	10 (5)
Nose bleeds	13 (9)	8 (5)	4 (2)
Stuffy nose	16 (11)	8 (5)	4 (2)
Lower respiratory [*n* (%)]	29 (19)	29 (19)	27 (14)
Asthma/COPD	16 (11)	21 (14)	15 (8)
Chronic bronchitis	8 (5)	2 (1)	2 (1)
Chest wheeze/whistling	6 (4)	9 (6)	7 (4)
Shortness of breath	8 (5)	7 (5)	8 (4)
Chest tightness	4 (3)	6 (4)	5 (3)
Cardiac [*n* (%)]	46 (31)	39 (26)	37 (19)
High blood pressure	38 (25)	33 (22)	29 (15)
Chest pain	8 (5)	5 (3)	6 (3)
Heart palpitations	10 (7)	7 (5)	4 (2)
Ankle swelling	11 (7)	5 (3)	5 (3)
Gastrointestinal [*n* (%)]	15 (10)	13 (9)	11 (6)
Ulcers/stomach problems	11 (7)	7 (5)	8 (4)
Liver problems	4 (3)	0 (0)	1 (0.5)
Nausea/vomiting	1 (1)	3 (2)	1 (0.5)
Abdominal pain	4 (3)	2 (1)	2 (1)
Diarrhea	5 (3)	2 (1)	2 (1)
Bleeding	4 (3)	4 (3)	0 (0)
Neurologic [*n* (%)]	48 (32)	37 (25)	39 (20)
Neurologic problems	1 (0.7)	5 (3)	0 (0)
Severe headache/migraine	24 (16)	14 (9)	18 (9)
Dizziness/balance problems	11 (7)	12 (8)	11 (6)
Depression	4 (3)	3 (2)	2 (1)
Difficulty concentrating/remembering	9 (6)	9 (6)	6 (3)
Difficulty sleeping/insomnia	18 (12)	19 (13)	10 (5)
Anxiety/nervousness	11 (7)	4 (3)	11 (6)
Seizures	2 (1)	2 (1)	1 (0.5)

COPD, chronic obstructive pulmonary disease.
[a]Six categories representing major health conditions of *a priori* interest chosen to ascertain symptom prevalence among individuals living in proximity to the nearest gas well in 2011–2012.

Table 3. Associations of nearest gas well proximity and symptoms.

Outcome	< 1 km OR (95% CI)	< 1 km *p*-Value	1–2 km OR (95% CI)	1–2 km *p*-Value	> 2 km
Dermal	4.13 (1.38, 12.3)	0.011	1.44 (0.42, 4.9)	0.563	Ref
Upper respiratory	3.10 (1.45, 6.65)	0.004	1.76 (0.81, 3.76)	0.148	Ref
Lower respiratory	1.45 (0.67, 3.14)	0.339	1.40 (0.65, 3.03)	0.387	Ref
Cardiac	1.67 (0.85, 3.26)	0.135	1.28 (0.65, 2.52)	0.473	Ref
Gastrointestinal	2.01 (0.49, 8.18)	0.328	1.79 (0.43, 7.41)	0.417	Ref
Neurological	1.53 (0.89, 2.63)	0.123	1.04 (0.59, 1.82)	0.885	Ref

Ref, reference. Results are from hierarchical logistic regression that adjusted for age, household education level, sex, smokers in household, job type, animals in household, and awareness of environmental risk.

Our findings of increased reporting of upper respiratory symptoms among persons living < 1 km from a natural gas well suggests that airborne irritant exposures related to natural gas extraction activities could be playing a role. Such irritant exposures could result from a number of activities related to natural gas drilling, including flaring of gas wells and exhaust from diesel equipment. Because other studies have suggested that airborne exposures could be a significant consequence of natural gas drilling activity, further investigation of the impact of such activities on respiratory health of nearby communities should be investigated. Future studies should collect such data.

Since most of the gas wells in the study area had been drilled in the past 5–6 years, one would not yet expect to see associations with diseases with long latency, such as cancer. Furthermore, if some of the impact of natural gas extraction on ground water happens over a number of years, this initial survey could have failed to detect health consequences of delayed contamination. However, if the finding of skin and respiratory conditions near gas wells indicates significant exposure to either fracking fluids and chemicals or airborne contaminants from natural gas wells, studies looking at such long-term health effects in chronically exposed populations would be indicated.

Conclusions

The results of this study suggest that natural gas drilling activities could be associated with increased reports of dermal and upper respiratory symptoms in nearby communities; these results support the need for further research into health effects of natural gas extraction activities. Such research could include longitudinal assessment of the health of individuals living in proximity to natural gas drilling activities, medical confirmation of health conditions, and more precise assessment of contaminant exposures.

References

Allen DT. 2014. Atmospheric emissions and air quality impacts from natural gas production and use. Annu Rev Chem Biomol Eng 5:55–75.

Bamberger M, Oswald RE. 2012. Impacts of gas drilling on human and animal health. New Solut 22:51–77.

Carter KM, Harper JA, Schmid KW, Kostelnik J. 2011. Unconventional natural gas resources in Pennsylvania: the backstory of the modern Marcellus Shale play. Environ Geosci 18:217–257.

Center for Rural Pennsylvania. 2014. Demographics for Washington County. Available: http://www.ruralpa2.org/county_profiles.cfm [accessed 29 July 2014].

Chapman EC, Capo RC, Stewart BW, Kirby CS, Hammack RW, Schroeder KT, et al. 2012. Geochemical and strontium isotope characterization of produced waters from Marcellus Shale natural gas extraction. Environ Sci Technol 46:3545–3553.

Chaumont A, Voisin C, Sardella A, Bernard A. 2012. Interactions between domestic water hardness, infant swimming and atopy in the development of childhood eczema. Environ Res 116:52–57.

Ferrar KJ, Kriesky J, Christen CL, Marshall LP, Malone SL, Sharma RK, et al. 2013. Assessment and longitudinal analysis of health impacts and stressors perceived to result from unconventional shale gas development in the Marcellus Shale region. Int J Occup Environ Health 19:104–112.

Goldstein BD, Kriesky J, Pavliakova B. 2012. Missing from the table: role of the environmental public health community in governmental advisory commissions related to Marcellus Shale drilling. Environ Health Perspect 120:483–486; doi:10.1289/ehp.1104594.

Jackson RB, Vengosh A, Darrah TH, Warner NR, Down A, Poreda RJ, et al. 2013. Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. Proc Natl Acad Sci USA 110:11250–11255.

Jackson RE, Gorody AW, Mayer B, Roy JW, Ryan MC, Van Stempvoort DR. 2013. Groundwater protection and unconventional gas extraction: the critical need for field-based hydrogeological research. Ground Water 51:488–510.

Kovats S, Depledge M, Haines A, Fleming LE, Wilkinson P, Shonkoff SB, et al. 2014. The health implications of fracking. Lancet 383:757–758.

Lampi P, Vohlonen I, Tuomisto J, Heinonen OP. 2000. Increase of specific symptoms after long-term use of chlorophenol polluted drinking water in a community. Eur J Epidemiol 16:245–251.

McDermott-Levy R, Kaktins N. 2012. Preserving health in the Marcellus region. Pa Nurse 67:4–10.

McKenzie LM, Witter RZ, Newman LS, Adgate JL. 2012. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ 424:79–87.

McNally NJ, Williams HC, Phillips DR, Smallman-Raynor M, Lewis S, Venn A, et al. 1998. Atopic eczema and domestic water hardness. Lancet 352:527–531.

Mitka M. 2012. Rigorous evidence slim for determining health risks from natural gas fracking. JAMA 307:2135–2136.

Myers T. 2012. Potential contaminant pathways from hydraulically fractured shale to aquifers. Ground Water 50:872–882.

Olaguer EP. 2012. The potential near-source ozone impacts of upstream oil and gas industry emissions. J Air Waste Manag Assoc 62:966–977.

Osborn SG, Vengosh A, Warner NR, Jackson RB. 2011. Methane contamination of drinking water accompanying gas-well drilling and hydraulic fracturing. Proc Natl Acad Sci USA 108:8172–8176.

PADEP (Pennsylvania Department of Environmental Protection). 2012. Homepage. Available: https://www.paoilandgasreporting.state.pa.us/publicreports/Modules/DataExports/DataExports.aspx [accessed 12 January 2012].

PASDA (Pennsylvania Spatial Data Access). 2013. Coal Mining Operations. Available: www.pasda.psu.edu/uci/SearchResults.aspx?originator=Pennsylvania Department of Environmental Protection&Keyword=&searchType=originator&entry=PASDA [accessed 12 October 2012].

Rozell DJ, Reaven SJ. 2012. Water pollution risk associated with natural gas extraction from the Marcellus Shale. Risk Anal 32:1382–1393.

Schabenberger O. 2007. Growing Up Fast: SAS® 9.2 Enhancements to the GLIMMIX Procedure. Paper 177-2007. Cary, NC:SAS Institute Inc. Available: http://www2.sas.com/proceedings/forum2007/177-2007.pdf [accessed 8 December 2014].

Steinzor N, Subra W, Sumi L. 2013. Investigating links between shale gas development and health impacts through a community survey project in Pennsylvania. New Solut 23:55–83.

U.S. Bureau of Labor Statistics. 2014. 2010 Census Occupational Classification. Available: http://www.bls.gov/cps/cenocc2010.htm [accessed 31 July 2014].

U.S. Department of Agriculture. 2007. Census of Agriculture. National Agriculture Statistics Service. Available: http://www.agcensus.usda.gov/index.php [accessed 10 January 2014].

Vidic RD, Brantley SL, Vandenbossche JM, Yoxtheimer D, Abad JD. 2013. Impact of shale gas development on regional water quality. Science 340:1235009; doi:10.1126/science.1235009.

Warner NR, Jackson RB, Darrah TH, Osborn SG, Down A, Zhao K, et al. 2012. Geochemical evidence for possible natural migration of Marcellus Formation brine to shallow aquifers in Pennsylvania. Proc Natl Acad Sci USA 109:11961–11966.

Witter RZ, McKenzie L, Stinson KE, Scott K, Newman LS, Adgate J. 2013. The use of health impact assessment for a community undergoing natural gas development. Am J Public Health 103:1002–1010.

Yorifuji T, Noguchi M, Tsuda T, Suzuki E, Takao S, Kashima S, et al. 2012. Does open-air exposure to volatile organic compounds near a plastic recycling factory cause health effects? J Occup Health. 54:79–87.

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1408133.

Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case–Control Analysis within the Nurses' Health Study II Cohort

Raanan Raz,[1] Andrea L. Roberts,[2] Kristen Lyall,[3,4] Jaime E. Hart,[1,5] Allan C. Just,[1] Francine Laden,[1,5,6] and Marc G. Weisskopf[1,6]

[1]Department of Environmental Health, [2]Department of Social and Behavioral Sciences, and [3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [4]Department of Public Health Sciences, University of California, Davis, Davis, California, USA; [5]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [6]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Background: Autism spectrum disorder (ASD) is a developmental disorder with increasing prevalence worldwide, yet has unclear etiology.

Objective: We explored the association between maternal exposure to particulate matter (PM) air pollution and odds of ASD in her child.

Methods: We conducted a nested case–control study of participants in the Nurses' Health Study II (NHS II), a prospective cohort of 116,430 U.S. female nurses recruited in 1989, followed by biennial mailed questionnaires. Subjects were NHS II participants' children born 1990–2002 with ASD (n = 245), and children without ASD (n = 1,522) randomly selected using frequency matching for birth years. Diagnosis of ASD was based on maternal report, which was validated against the Autism Diagnostic Interview-Revised in a subset. Monthly averages of PM with diameters ≤ 2.5 μm ($PM_{2.5}$) and 2.5–10 μm ($PM_{10-2.5}$) were predicted from a spatiotemporal model for the continental United States and linked to residential addresses.

Results: $PM_{2.5}$ exposure during pregnancy was associated with increased odds of ASD, with an adjusted odds ratio (OR) for ASD per interquartile range (IQR) higher $PM_{2.5}$ (4.42 μg/m^3) of 1.57 (95% CI: 1.22, 2.03) among women with the same address before and after pregnancy (160 cases, 986 controls). Associations with $PM_{2.5}$ exposure 9 months before or after the pregnancy were weaker in independent models and null when all three time periods were included, whereas the association with the 9 months of pregnancy remained (OR = 1.63; 95% CI: 1.08, 2.47). The association between ASD and $PM_{2.5}$ was stronger for exposure during the third trimester (OR = 1.42 per IQR increase in $PM_{2.5}$; 95% CI: 1.09, 1.86) than during the first two trimesters (ORs = 1.06 and 1.00) when mutually adjusted. There was little association between $PM_{10-2.5}$ and ASD.

Conclusions: Higher maternal exposure to $PM_{2.5}$ during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.

Citation: Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, Weisskopf MG. 2015. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: a nested case–control analysis within the Nurses' Health Study II cohort. Environ Health Perspect 123:264–270; http://dx.doi.org/10.1289/ehp.1408133

Introduction

Autism spectrum disorder (ASD) is a developmental disorder with increasing reported prevalence worldwide (French et al. 2013). Although genetics plays a strong role in ASD, evidence suggests that environmental exposures, particularly *in utero* or during early life, also affect ASD risk (Grønborg et al. 2013; Hallmayer et al. 2011; Quaak et al. 2013). However, no specific environmental toxicant has been consistently associated with increased risk of ASD.

Air pollution contains various toxicants that have been found to be associated with neurotoxicity and adverse effects on the fetus *in utero* (Crump et al. 1998; Grandjean and Landrigan 2006; Rice and Barone 2000; Rodier 1995; Stillerman et al. 2008). Airborne particles are covered with various contaminants, and have been found to penetrate the subcellular environment and induce oxidative stress and mitochondrial damage *in vitro* (Li et al. 2003; MohanKumar et al. 2008). In rodents, these particles also have been found to stimulate inflammatory cytokine release systemically and in the brain, and alter the neonatal immune system (Hertz-Picciotto et al. 2005, 2008; MohanKumar et al. 2008)—processes that have been implicated in ASD (Depino 2013; Napoli et al. 2013).

Several studies have explored associations of air pollution with ASD, using the U.S. Environmental Protection Agency (EPA) hazardous air pollutant models, distance to freeway, or local models for specific pollutants. These studies suggest increased odds of having a child with ASD with higher exposures to diesel particulate matter (PM) (Roberts et al. 2013; Windham et al. 2006), several metals (Roberts et al. 2013; Windham et al. 2006), criteria pollutants (Becerra et al. 2013; Volk et al. 2013), and some organic materials as well as closer proximity to a freeway (Volk et al. 2011).

Our goal was to explore the association between ASD and exposure to PM during defined time periods before, during, and after pregnancy, within the Nurses' Health Study II (NHS II), a large, well-defined cohort with detailed residential history. This nested case–control study includes participants from across the continental United States, and exposure was linked to monthly data on two size fractions of PM.

Methods

Participants. The study population included offspring of participants in NHS II, a prospective cohort of 116,430 U.S. female nurses 25–43 years of age when recruited in 1989, followed biennially (Solomon et al. 1997). NHS II participants originally were recruited from 14 states in all regions of the continental United States, but they now reside in all 50 states. The study was approved by the Partners Health Care Institutional Review Board and complied with all applicable U.S. regulations; return of completed questionnaires constituted consent to participate.

In 2005, NHS II participants were asked whether any of their children had been diagnosed with autism, Asperger's syndrome, or "other autism spectrum," and 839 women replied affirmatively. In 2007, we initiated a pilot follow-up study, shortly followed by a full-scale follow-up as described previously (Lyall et al. 2012). The follow-up questionnaire included questions about the pregnancy and birth, child's sex, and diagnosis. NHS II protocol allows re-contacting only the nurses who responded to the most recent

Address correspondence to R. Raz, Harvard T.H. Chan School of Public Health, 401 Park Dr., Landmark Center, P.O. Box 15697, Boston, MA 02215 USA. Telephone: (617) 735-5554. E-mail: rraz@hsph.harvard.edu

We acknowledge M. Power, M.-A. Kioumourtzoglou, and R. Seals for discussions that enhanced this study.

The study was supported by a postdoctoral fellowship to R.R. from the Environment and Health Fund (EHF, Israel); National Institutes of Health grants P30 ES000002, R01 ES017017, and UM1 CA176726; U.S. Department of Defense grant W81XWH-08-1-0499; and Autism Speaks Foundation grant 1788.

The authors declare they have no actual or potential competing financial interests.

Received: 15 January 2014; Accepted: 10 December 2014; Advance Publication: 18 December 2014; Final Publication: 1 March 2015.

biennial questionnaire. Thus, this follow-up was attempted with the 756 mothers of ASD cases for whom this was the case. Mothers who reported having more than one child with ASD were directed to report about the youngest one. Controls were selected from among parous women not reporting a child with ASD in 2005. For each case mother, controls were randomly selected from among those women who gave birth to a child in a matching birth year, to yield a total of 3,000 controls. Six hundred thirty-six (84%) mothers of cases and 2,747 (92%) mothers of controls responded; 164 women (including 51 case mothers) declined to participate.

For the current study, only children whose estimated conception month was June 1989 or later were included because nurses' addresses before this month were unknown. Of the 265 children reported to have an ASD diagnosis who met this criterion we excluded 4 for whom ASD was not confirmed by the mother on the follow-up questionnaire, and another 2 with genetic syndromes associated with ASD (n = 1 Down syndrome; n = 1 Rett syndrome). The remaining 259 children were classified as ASD cases. There were 1,640 control children who met the conception month criterion. We further excluded participants missing PM data because their addresses could not be geocoded (8 cases and 30 controls), controls who were reported to have ASD on the 2009 questionnaire (n = 9), and children missing data on birth month (6 cases and 79 controls). The final study sample included 245 cases and 1,522 controls born 1990 through 2002. The average (± SD) year of diagnosis of the ASD cases was 1999 ± 3.3. None of these children were reported to have been adopted. Of 188 ASD cases with data on ASD in siblings, 7.4% were reported to have a sibling with ASD. Analyses excluding those 7.4% were similar to analyses including all children and are therefore not reported.

Case validation. ASD diagnosis was validated by telephone administration of the Autism Diagnostic Interview–Revised (ADI-R) (Lord et al. 1994) in a subsample of 50 cases randomly selected from mothers who indicated on our follow-up questionnaire willingness to be contacted (81% of all case mothers). In this sample, 43 children (86%) met full ADI-R criteria for autistic disorder [which is stricter than the broader "autism spectrum disorder" of the current DSM-V (*Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*) criteria, or other autism spectrum disorders including PDD-NOS (pervasive developmental disorder not otherwise specified) or Asperger syndrome of DSM-IV criteria], defined by meeting cutoff scores in all three domains (social interaction, communication and language, restricted and repetitive behaviors) and having onset by 3 years of age. The remaining individuals met the onset criterion and communication domain cutoff and missed the autistic disorder cutoff by one point in one domain (n = 5; 10%), or met cutoffs in one or two domains only (n = 2; 4%), thus indicating presence of ASD traits [for further details on scoring of ADI-R, see Lord et al. (1994)]. In addition, Social Responsiveness Scale (SRS) scores (Constantino et al. 2000), obtained for approximately 90% of eligible cases, also indicated accuracy of case ascertainment. Although it is not a clinical diagnostic instrument, the SRS is a widely used measure of social functioning and autistic traits, and has been shown to have excellent validity as compared to ADI-R and ADOS (Autism Diagnostic Observation Schedule) (Constantino et al. 2003). Among our ASD cases, 93% met the SRS cutoff for ASD. In contrast, 93% of controls completing the same measure fell within the normative range. Therefore, both ADI-R and SRS scores support reliable ASD case ascertainment in our population. For all analyses only the maternal reports were used for determination of ASD status.

Exposure assessment. Residential locations of the nurses were determined from the mailing addresses used for the biennial NHS II questionnaire. Monthly ambient exposure predictions of airborne particulate matter with an aerodynamic diameter ≤ 10 μm (PM_{10}) and ≤ 2.5 μm ($PM_{2.5}$) were generated from nationwide expansions of previously validated spatiotemporal models (Yanosky et al. 2008, 2009, 2014). The models use monthly average PM_{10} and/or $PM_{2.5}$ data from the U.S. EPA's Air Quality System (http://www.epa.gov/ttn/airs/airsaqs/), a nationwide network of continuous and filter-based monitors, as well as monitoring data from various other sources. The models also incorporated information on several geospatial predictors including distance to road, population density, point sources (e.g., power-generating utilities, waste combustors), elevation, and meteorology. All data were used in generalized additive statistical models (Yanosky et al. 2008) with smoothing terms of space and time to create separate PM prediction surfaces for each month. Because monitoring data on $PM_{2.5}$ are limited before 1999, $PM_{2.5}$ in the period before 1999 was modeled using data on PM_{10} and visibility data at airports (Yanosky et al. 2009, 2014). $PM_{10–2.5}$ predictions were calculated as the difference between monthly PM_{10} and $PM_{2.5}$ predictions. These models provide estimates for any geolocation in the conterminous United States by monthly intervals. The models also have been shown to have low bias and high precision: The normalized mean bias factor for $PM_{2.5}$ is –1.6%, and the absolute value of the prediction errors is 1.61. For $PM_{2.5–10}$ these values are –3.2% and 4.18, respectively (Yanosky et al. 2014).

For each child, we estimated exposures to $PM_{2.5}$ and $PM_{10–2.5}$ before, during, and after pregnancy by averaging monthly concentrations for the mother's residential address during the relevant months. The months of pregnancy were determined from the child's birth month and gestational age at birth, as reported by the mother. Exposures to PM during each pregnancy trimester were calculated similarly.

Covariates. The following covariates, all associated with autism in previous studies, were included in multivariable models: child's birth year, birth month, and sex, maternal age at birth, paternal age at birth, and median census tract income in the birth year. Among these variables, only census tract income (1.5%) and paternal age (10.6%) had missing data. We used the missing indicator method for missing data. We conducted sensitivity analyses to evaluate the influence of adjusting for gestational factors (premature birth, birth weight, gestational diabetes, preeclampsia), smoking during pregnancy, state, marital status, median census house value, paternal education, and maternal grandparents' education. All covariate data except for census variables were from maternal self-report.

Statistical analyses. Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) of ASD by PM exposures modeled both using PM quartiles and as continuous variables, in separate models. Exposures to different PM size fractions were examined in separate models, and also together in a single model.

For nurses who moved residence between two questionnaires straddling pregnancy, we did not know the exact date of moving. Therefore, we conducted separate analyses for exposures assigned assuming the nurse was at the earlier address during the whole intervening period (prepregnancy address) or at the later address during the whole period (postpregnancy address). In addition, to reduce misclassification of exposure, we conducted analyses that were limited to those mothers for whom the pre- and postpregnancy addresses were identical [160 cases (65%) and 986 controls (65%), referred to here as "nonmovers"].

To examine temporal specificity of any associations between PM and ASD, we considered the association with $PM_{2.5}$ exposure during the 9 months before pregnancy, the pregnancy period, and the 9 months after birth. These examinations were restricted to nonmovers with complete

Table 1. Study population characteristics by ASD status, Nurses' Health Study II.

Characteristic	Cases (n = 245)	Controls (n = 1,522)
Male sex [n (%)]	209 (85)	793 (52)
Year of birth [median (IQR)]	1993 (5)	1993 (5)
Maternal age at birth (years) (mean ± SD)	34.0 ± 4.0	33.7 ± 3.7
Paternal age at birth (years) (mean ± SD)	36.8 ± 5.3	36.3 ± 4.9
Median census income ($1,000) [median (IQR)]	63 (26)	61 (27)
Median census house value ($1,000) [median (IQR)]	144 (108)	136 (98)
Birth weight (lbs) (mean ± SD)	7.1 ± 1.5	7.2 ± 1.3
Husband's/partner's education [n (%)]		
High school	33 (13)	208 (14)
2-year college	45 (18)	218 (14)
4-year college	79 (32)	537 (35)
Graduate school	74 (30)	501 (33)
Missing	14 (6)	58 (4)
Marital status [n (%)]		
Married	186 (76)	1,159 (76)
Never married	51 (21)	269 (18)
Other	8 (3)	94 (6)
Premature birth [n (%)]		
Yes	44 (18)	227 (15)
No	142 (58)	1,137 (75)
Missing	59 (24)	158 (10)
Gestational diabetes [n (%)]		
Yes	17 (7)	87 (6)
No	189 (77)	1,222 (80)
Missing	39 (16)	213 (14)
Preeclampsia [n (%)]		
Yes	13 (5)	43 (3)
No	193 (79)	1,266 (83)
Missing	39 (16)	213 (14)
Smoking during pregnancy [n (%)]		
Yes	22 (9)	50 (3)
No	160 (65)	1,099 (72)
Missing	63 (26)	373 (25)

IQR, Interquartile range.

Table 2. Control population characteristics by pregnancy $PM_{2.5}$ quartile, Nurses' Health Study II (n = 1,522 controls).

	Quartile [μg/m^3 (range)]			
Characteristic	1st (5.24–12.3)	2nd (12.4–14.5)	3rd (14.6–16.7)	4th (16.7–30.8)
n	397	376	375	374
Male sex (n (%)]	208 (52)	203 (54)	192 (51)	190 (51)
Year of birth [median (IQR)]	1995 (5)	1994 (4)	1993 (4)	1992 (3)
Maternal age at birth (years) (mean ± SD)	34.3 ± 3.8	34.0 ± 3.8	33.5 ± 3.6	32.7 ± 3.6
Paternal age at birth (years) (mean ± SD)	37.4 ± 5.1	36.5 ± 4.9	36.1 ± 5.0	35.2 ± 4.5
Median census income ($1,000) [median (IQR)]	62 (31)	64 (28)	61 (26)	58 (24)
Median census house value ($1,000) [median (IQR)]	137 (107)	144 (104)	135 (96)	128 (82)
Birth weight (lbs) (mean ± SD)	7.2 ± 1.3	7.2 ± 1.2	7.1 ± 1.3	7.2 ± 1.3
Premature birth (n (%)]				
Yes	56 (14)	57 (15)	52 (14)	62 (17)
No	298 (75)	282 (75)	275 (73)	282 (75)
Missing	43 (11)	36 (10)	48 (13)	30 (8)
Gestational diabetes (n (%)]				
Yes	18 (5)	27 (7)	21 (6)	21 (6)
No	314 (79)	303 (81)	299 (80)	306 (82)
Missing	65 (16)	46 (12)	55 (15)	47 (13)
Preeclampsia (n (%)]				
Yes	12 (3)	9 (2)	8 (2)	14 (4)
No	320 (81)	321 (85)	312 (83)	313 (84)
Missing	65 (16)	46 (12)	55 (15)	47 (13)
Smoking during pregnancy (n (%)]				
Yes	17 (4)	17 (4)	21 (5)	17 (4)
No	323 (73)	313 (71)	308 (70)	315 (71)
Missing	102 (23)	112 (25)	112 (25)	110 (25)

IQR, interquartile range.

data for all exposure periods, and each time period was considered independently, and then also in a single model that included all three time periods simultaneously. Because of differences in ASD rates by sex and prior suggestions that air pollution effects may be specific to boys, we *a priori* decided to also examine associations stratified by sex of the child. For simplicity, we did this only among the children whose mothers did not move during pregnancy. We used SAS version 9.3 (SAS Institute Inc., Cary, NC) for data extraction, and R version 3.0.1 (http://www.r-project.org/foundation/) for Linux-gnu for analyses. All analyses were conducted at the 0.05 alpha level.

Results

ASD cases were more likely to be male, to have been exposed to maternal preeclampsia or maternal smoking during gestation, and to be missing data on premature birth compared with controls (Table 1). The median (25th–75th percentile) year of birth for cases and controls was the same: 1993 (1991–1996). As expected given time trends in air pollution, control children born in earlier years were more likely to be in higher $PM_{2.5}$ quartiles. Census income and parental age also decreased slightly, but generally steadily by exposure, whereas there was little clear pattern of difference by exposure for other variables (Table 2).

The average (± SD) levels of $PM_{2.5}$ and $PM_{10-2.5}$ during pregnancy were 14.6 ± 3.3 and 9.9 ± 4.9 μg/m^3, respectively. Although $PM_{10-2.5}$ did not show a clear and consistent association with ASD, $PM_{2.5}$ was associated with ASD regardless of the address used for the PM estimation (Figure 1). Among nonmovers, for whom misclassification of exposure because of an address change is reduced, the OR was 2.06 (95% CI: 1.17, 3.63) in the 4th quartile, compared with the 1st quartile. The results were also similar when analysis was limited to nonmovers and used continuous PM estimates, with an OR of 1.57 (95% CI: 1.22, 2.03) per interquartile range (IQR) increase in $PM_{2.5}$ (4.42 μg/m^3), and little association with $PM_{10-2.5}$ [OR = 1.07 per $PM_{10-2.5}$ IQR (5.15 μg/m^3); 95% CI: 0.89, 1.28]. When $PM_{2.5}$ and $PM_{10-2.5}$ were in the same model together, the difference between the two was greater: OR = 1.61 per $PM_{2.5}$ IQR (95% CI: 1.22, 2.12); OR = 0.96 per $PM_{10-2.5}$ IQR (95% CI: 0.79, 1.17). The association with $PM_{2.5}$ among nonmovers was slightly stronger for boys (OR = 1.73; 95% CI: 1.29, 2.31) than for girls (OR = 1.12; 95% CI: 0.59, 2.12), but there were only 23 nonmover girls with ASD (137 nonmover boys), and the interaction p-value was 0.17.

When estimating the association with $PM_{2.5}$ exposure during the 9 months before pregnancy, the pregnancy period, and the 9 months after birth, all restricted to nonmovers with exposure estimates for all three exposure periods, the associations with exposures before or after the pregnancy were lower compared with the association with exposure during pregnancy (Table 3). The partial correlation of $PM_{2.5}$ during pregnancy with $PM_{2.5}$ during the 9 months before or after pregnancy was 0.85 and 0.83, respectively. When we included all three $PM_{2.5}$ exposure periods together in a mutually adjusted model, ASD was significantly associated only with exposure during the pregnancy period (Table 3). This pattern did not change after further restriction to women who did not move during the whole period from 9 months before conception to 9 months after birth (data not shown).

When examining trimester-specific associations in nonmovers, exposure to $PM_{2.5}$ was associated with ASD in all three trimesters, but $PM_{10–2.5}$ was not associated with ASD in any of the trimesters (Figure 2). The highest association with $PM_{2.5}$ was seen in the third trimester (OR = 1.49 per $PM_{2.5}$ IQR; 95% CI: 1.20, 1.85) (Figure 2). In a model with all trimesters mutually adjusted, the only statistically significant association was seen with $PM_{2.5}$ in the third trimester (OR = 1.42; 95% CI: 1.09, 1.86), whereas exposure during the first and second did not show associations (OR = 1.06; 95% CI: 0.83, 1.35, and OR = 1.00; 95% CI: 0.78, 1.30, respectively). When third-trimester $PM_{2.5}$ and $PM_{10–2.5}$ were in the same model together, the difference between the two was greater: OR = 1.50 per $PM_{2.5}$ IQR (95% CI: 1.19, 1.89); OR = 0.89 per $PM_{10–2.5}$ IQR (95% CI: 0.81, 1.19).

ORs and CIs were comparable in separate analyses excluding premature births, or participants missing data on census tract income, or paternal age (data not shown). Adjusting for $PM_{10–2.5}$ also resulted in comparable estimates for $PM_{2.5}$ (data not shown). Results were also similar in models adjusted for (each in a separate model): gestational variables (premature birth, birth weight, gestational diabetes, preeclampsia), smoking during pregnancy, census tract house value, state, marital status of the nurse, or husband's/partner's education or maternal grandparents' education (data not shown). In addition, models limited to either mothers with white race/ethnicity (95% of the nurses) or children who had a full-term pregnancy (i.e., excluding premature births and those with missing data on this variable) showed comparable estimates (data not shown).

Discussion

In our nested case–control study of nurses from across the continental United States, ambient $PM_{2.5}$ concentrations during pregnancy were significantly associated with having a child diagnosed with ASD. Importantly, the association we found appeared specific to $PM_{2.5}$ during pregnancy; $PM_{2.5}$ exposure before or after pregnancy showed weaker associations with ASD, and $PM_{10–2.5}$ during pregnancy showed little association with ASD. In a model mutually adjusted for all three exposure periods, only the pregnancy period was associated with ASD. The change in the ORs with mutual adjustment did not appear to be an artifact of collinearity because the precision of the mutually adjusted model was not substantially lower than the single exposure model (e.g., CI widths for an IQR change in $PM_{2.5}$ during pregnancy of 2.3 vs. 1.7, respectively). The 95% CIs were not notably larger in this analysis, suggesting that collinearity was not a significant problem. Moreover, during pregnancy we found the association to be specifically with the third-trimester exposure in models that included exposure in all trimesters together. The specificity of the association to the prenatal period is in line with several other lines of evidence that suggest a prenatal origin of ASD, including data on differences in brain cytoarchitecture in brains of children with ASD (McFadden and Minshew 2013; Stoner et al. 2014) and associations between maternal exposure to teratogens during pregnancy and ASD (Rodier 1995). Our results also suggest an association predominantly in boys, but this finding should be interpreted with caution, given the small number of girls with ASD in our sample.

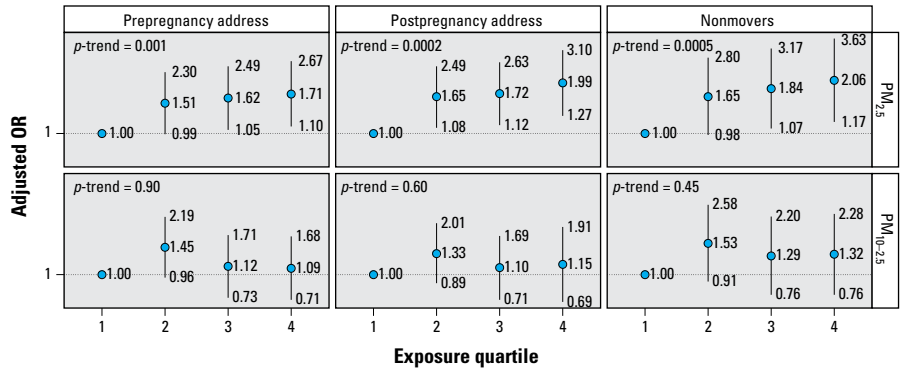


Figure 1. ORs (95% CIs) for ASD by quartile of PM exposure. ORs are adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, and census income. There were 245 cases and 1,522 controls in analyses using pre- and postpregnancy addresses. Prepregnancy address is the last known residential address before conception. Postpregnancy address is the first known residential address after birth. Nonmovers are those participants for whom prepregnancy and postpregnancy addresses were the same [cases = 160 (65%), controls = 986 (65%)]. *p*-Trend, *p*-values from models of exposures as continuous variables. The number of cases (including movers) by quartiles from low to high: 45, 66, 66, 68; controls: 397, 376, 375, 374. $PM_{2.5}$ quartile ranges (μg/m^3): 5.24–12.3, 12.4–14.5, 14.6–16.7, 16.7–30.8; $PM_{10–2.5}$ quartile ranges (μg/m^3): 1.9–6.7, 6.8–8.9, 9–11.9, 12–49.4.

Table 3. ORs (95% CI) for ASD per IQR increase in $PM_{2.5}$ levels in different time periods, nonmovers only.[a]

Exposure period	OR (95% CI) per 4.40 μg/m^3 $PM_{2.5}$		
	Unadjusted	Adjusted[b]	Mutually adjusted[c]
9 months before conception	1.20 (0.98, 1.47)	1.32 (1.04, 1.69)	0.83 (0.58, 1.19)
Whole pregnancy	1.37 (1.09, 1.71)	1.50 (1.16, 1.94)	1.63 (1.08, 2.47)
9 months after birth	1.19 (0.96, 1.49)	1.29 (1.00, 1.67)	0.96 (0.65, 1.40)

[a]Restricted to nonmovers who also have data on all exposure periods (158 cases, 977 controls). [b]Adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, census income. [c]Mutually adjusted for other two exposure periods, as well as all other covariates listed above.

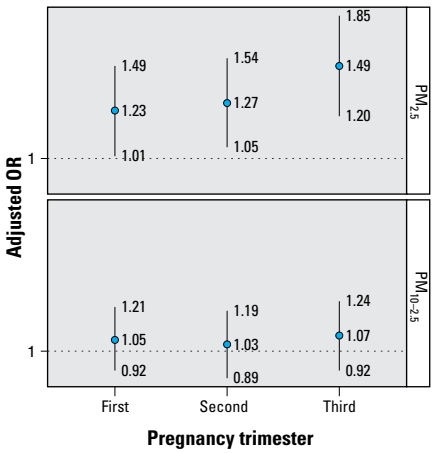


Figure 2. ORs for ASD with exposure to particulate matter during pregnancy trimesters. ORs are adjusted for child sex, year of birth, month of birth, maternal age at birth, paternal age at birth, and census income. The analyses are limited to nonmovers only (i.e., those for whom prepregnancy and postpregnancy addresses were the same). Cases, *n* = 160, controls *n* = 986.

These results generally agree with previous studies. A report from the CHildhood Autism Risks from Genetics and the Environment (CHARGE) study among 304 ASD cases and 259 controls, in several areas in California, used residential address history reported by parents to calculate distance to roads as a proxy for traffic-related air pollution exposure and found increased risk for ASD among women who lived in proximity to a freeway (Volk et al. 2011). Further analysis of the CHARGE study group in a subset of 279 cases and 245 controls using data from the U.S. EPA Air Quality System suggested positive associations of ASD with traffic-related air pollution during pregnancy, and specifically with $PM_{2.5}$ (Volk et al. 2013). ASD was also associated with pregnancy exposure to PM_{10}, and—in contrast to our results—the association with traffic-related air pollution exposure during the first year of life was higher than that found for the exposure during pregnancy. In the CHARGE study, associations were also seen with exposures in the year after birth that were about as strong as exposures during pregnancy. Our findings suggested a weaker association with postpregnancy exposure that was essentially null in models that included exposure during all time periods. In the CHARGE study, however, the pregnancy and postpregnancy exposure periods were not included together in the same regression model.

Another study, from Los Angeles (LA) County, used birth certificate address and ASD cases identified from the Department of Developmental Services in California (Becerra et al. 2013). Using exposure data from the nearest monitoring stations and from a land use regression model (Su et al. 2009), they found a positive association between $PM_{2.5}$ exposure and autism (OR per 4.68 $\mu g/m^3$ $PM_{2.5}$ = 1.15; 95% CI: 1.06, 1.24 in a model of exposure over the entire pregnancy and also adjusted for ozone levels). There was not a consistent association with PM_{10}. The LA study included many more ASD cases than any of the other studies, so the effect estimate could represent a more stable estimate of the true effects of PM. Alternatively, differences in the composition of PM in the LA area could result in smaller effects. Other differences in study design could also have led to smaller effect sizes in the LA study. The case definition was a primary diagnosis of autistic disorder, the most severe among ASD diagnoses, and the association with PM could be preferentially with milder forms of ASD. Slightly more measurement error from using a nearest monitor exposure assignment approach or addresses from the birth certificate could have biased results toward the null. Smaller associations in that study could also have occurred if there was under-ascertainment of cases among children of more highly exposed mothers. Lower socioeconomic status has been associated with under-ascertainment in ASD registries such as that used in the LA study (Kalkbrenner et al. 2012). Although estimates were not much different when the sample was stratified by education level, if residual socioeconomic differences were associated with $PM_{2.5}$ exposures (lower socioeconomic status with higher $PM_{2.5}$) this could lead to bias toward the null because the controls included all birth certificates in the region. The importance of the environment in the development of ASD was recently implicated in a comparison of concordance rates between monozygotic and dizygotic twins that found that the shared environment accounted for 58% (95% CI: 30, 80%) of the broader autism phenotype (Hallmayer et al. 2011). In line with these findings, a comparison of sibling ASD recurrence risk in a different population revealed a much higher rate of ASD recurrence in half-siblings with the same mother (2.4; 95% CI: 1.4, 4.1) compared with half-siblings with the same father (1.5; 95% CI: 0.7, 3.4) (Grønborg et al. 2013). This finding may be attributed either to maternal factors affecting the *in utero* environment or to common mitochondrial DNA.

Exposure to high levels of environmental toxicants during pregnancy might interfere with normal *in utero* processes of brain development, such as neurogenesis, cell proliferation, cell differentiation, and apoptosis (Rice and Barone 2000; Rodier 1995). $PM_{2.5}$ and especially ultrafine particles (< 0.1 μm in diameter) were shown to penetrate the subcellular environment and to induce strong oxidative stress and mitochondrial damage *in vitro* (Li et al. 2003). These effects were associated with the organic carbon and polycyclic aromatic hydrocarbon contents of the particles (Li et al. 2003). *In vivo* studies in rodents have also shown that $PM_{2.5}$ activates the stress axis, involves microglial activation, and causes production of pro-inflammatory cytokines in the brain (MohanKumar et al. 2008). In one study, increased mitochondrial DNA damage, possibly caused by reactive oxygen species, was found to be more common in 67 children with ASD than in 46 typically developing children (Napoli et al. 2013).

$PM_{2.5}$ may alter the development of the neonatal immune system. In a study of 1,397 children in the Czech Republic, gestational exposures to $PM_{2.5}$ and polycyclic aromatic hydrocarbons were associated with reduction in T cells and an increase in B lymphocytes in neonatal cord blood (Hertz-Picciotto et al. 2005). Early activation of the immune system and neuroinflammation have been found to be associated with ASD in humans (Atladóttir et al. 2010; Careaga et al. 2013; Depino 2013; Gadad et al. 2013; Libbey et al. 2005; Patterson 2011) and in animal models of autism (Gadad et al. 2013; Libbey et al. 2005; Patterson 2011), and this has been proposed as a possible mechanism by which environmental toxicants could increase the risk of ASD (Hertz-Picciotto et al. 2008). Furthermore, a recent transcriptomic comparison of post-mortem brain tissues of individuals with ASD (n = 19) and controls (n = 17) taken from the Autism Tissue Project, the Harvard Brain Bank, and the MRC London Brain Bank for Neurodegenerative Disease, revealed involvement of genes related to synaptic and neuronal signaling dysfunction, and also microglial and immune dysregulation (Voineagu et al. 2011). The implicated genes related to synaptic and neuronal signaling dysfunction, compared with those related to immune changes, had more overlap with genes identified in genome-wide association studies (Voineagu et al. 2011). This suggests that expression of immune-related genes in ASD may be driven more by environmental influences than underlying genetic differences.

These processes that could affect neurodevelopment are general in nature, so the question still would remain why there is an association specifically with ASD. However, the ASD phenotype is quite heterogeneous, and ASD can share features with other neurodevelopmental disorders (e.g., intellectual disability). There is some suggestion that exposures to components of air pollution can also affect neurodevelopment more generally (Perera et al. 2009; Suglia et al. 2008). Determining the range of phenotypic profiles associated with maternal PM exposure during pregnancy would be of interest in future studies. Another interesting direction for future research would be to determine whether the association between PM and ASD is different among children who have one or more siblings with ASD.

A limitation of our study is that we did not have the exact dates on which mothers changed addresses. Thirty-five percent of the nurses (both cases and controls) changed their residential address between the last questionnaire before pregnancy and the first questionnaire after delivery. However, we found statistically significant associations with pregnancy PM when the exposure for movers was based either on pre- or postpregnancy address. When we reduced exposure misclassification by analyzing the smaller sample of nonmovers, the association between ASD and $PM_{2.5}$ was stronger. We also did not have information on how much time the nurses actually spent at their residential addresses, nor did we have information about their work addresses. Error from this source, however, would not affect the estimates of PM at the residential address and so would not create an association with

residential PM levels where an association with PM exposure did not exist. Information was also unavailable on indoor air pollution exposures and sources. In addition, ASD diagnoses in the study were based on parental reporting. As medically trained professionals, however, nurse mothers' reporting of ASD is likely to be reliable, a supposition supported by our validation study using the ADI-R.

Strengths of our study include the wide geographic distribution of the nurses and the nesting within a well-defined cohort, which reduces the likelihood of selection bias. In addition, the specificity of our findings for the pregnancy period places important limitations on possible residual confounding. Specifically, any factor that is not differentially related to PM during pregnancy versus before or after pregnancy is very unlikely to confound our results. Thus, for example, although population density, a choice to take folate supplements during pregnancy, or a host of other potential confounders (Gray et al. 2013; Kalkbrenner et al. 2012) may be related to $PM_{2.5}$ exposure, they would be expected to be equally related to $PM_{2.5}$ exposure before or after pregnancy as during it. But no association with them were seen in mutually adjusted models. In this way, $PM_{2.5}$ exposure before and after pregnancy (because no association is seen with them in mutually adjusted models) acts as a negative control (Flanders et al. 2011; Lipsitch et al. 2010) and rules out confounding by many—even unmeasured—potential confounders. We cannot, however, rule out another pollutant that co-varies with $PM_{2.5}$. Nor can we determine whether there is a particular component of $PM_{2.5}$ that is responsible for the associations we found. $PM_{2.5}$, however, is a complex mixture that may be correlated with other air pollution constituents. In the present study we did not have high temporal and spatial resolution data on other air pollution constituents or on specific $PM_{2.5}$ components to determine whether a specific component is associated with autism.

Conclusions

Our findings support the possibility of an effect of maternal exposure to air pollution during pregnancy, and especially during the third trimester, on the development of ASD in her child. The results suggest that air pollution is a modifiable risk factor for autism, and reduced exposure during pregnancy could lead to lower incidence of ASD and reduce the substantial, increasing economic burden of ASD on families and on society (Croen et al. 2006; Leslie and Martin 2007; Mandell et al. 2006; Raz et al. 2013; Shimabukuro et al. 2008). Understanding the biological mechanism that may underlie the association by which PM exposure and ASD could provide important insight to ASD pathogenesis.

References

Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, et al. 2010. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord 40:1423–1430; doi:10.1007/s10803-010-1006-y.

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. 2013. Ambient Air Pollution and Autism in Los Angeles County, California. Environ Health Perspect 121:380–386; doi:10.1289/ehp.1205827.

Careaga M, Hansen RL, Hertz-Piccotto I, Van de Water J, Ashwood P. 2013. Increased anti-phospholipid antibodies in autism spectrum disorders. Mediators Inflamm 2013:935608; doi:10.1155/2013/935608.

Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, et al. 2003. Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J Autism Dev Disord 33:427–433.

Constantino JN, Przybeck T, Friesen D, Todd RD. 2000. Reciprocal social behavior in children with and without pervasive developmental disorders. J Dev Behav Pediatr 21:2–11.

Croen LA, Najjar DV, Ray GT, Lotspeich L, Bernal P. 2006. A comparison of health care utilization and costs of children with and without autism spectrum disorders in a large group-model health plan. Pediatrics 118:e1203–e1211; doi:10.1542/peds.2006-0127.

Crump KS, Kjellström T, Shipp AM, Silvers A, Stewart A. 1998. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. Risk Anal 18:701–713.

Depino AM. 2013. Peripheral and central inflammation in autism spectrum disorders. Mol Cell Neurosci 53:69–76; doi:10.1016/j.mcn.2012.10.003.

Flanders WD, Klein M, Darrow LA, Strickland MJ, Sarnat SE, Sarnat JA, et al. 2011. A method for detection of residual confounding in time-series and other observational studies. Epidemiology 22:59–67; doi:10.1097/EDE.0b013e3181fdcabe.

French LR, Bertone A, Hyde KL, Fombonne E. 2013. Epidemiology of autism spectrum disorders. In: The Neuroscience of Autism Spectrum Disorders (Buxbaum JD, Hof PR, eds). New York:Academic Press, 3–24.

Gadad BS, Hewitson L, Young KA, German DC. 2013. Neuropathology and animal models of autism: genetic and environmental factors. Autism Res Treat 2013:731935; doi:10.1155/2013/731935.

Grandjean P, Landrigan PJ. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368:2167–78; doi:10.1016/S0140-6736(06)69665-7.

Gray SC, Edwards SE, Miranda ML. 2013. Race, socioeconomic status, and air pollution exposure in North Carolina. Env Res 126:152-8; doi:10.1016/j.envres.2013.06.005.

Grønborg TK, Schendel DE, Parner ET. 2013. Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study. JAMA Pediatr 167:947–953; doi:10.1001/jamapediatrics.2013.2259.

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. 2011. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 68:1095–1102; doi:10.1001/archgenpsychiatry.2011.76.

Hertz-Picciotto I, Herr CEW, Yap PS, Dostál M, Shumway RH, Ashwood P, et al. 2005. Air pollution and lymphocyte phenotype proportions in cord blood. Environ Health Perspect 113:1391–1398; doi:10.1289/ehp.7610.

Hertz-Picciotto I, Park HY, Dostal M, Kocan A, Trnovec T, Sram R. 2008. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic Clin Pharmacol Toxicol 102:146–154; doi:10.1111/j.1742-7843.2007.00190.x.

Kalkbrenner AE, Braun JM, Durkin MS, Maenner MJ, Cunniff C, Lee L, et al. 2012. Maternal smoking during pregnancy and the prevalence of autism spectrum disorders, using data from the autism and developmental disabilities monitoring network. Environ Health Perspect 120:1042–1048; doi:10.1289/ehp.1104556.

Leslie DL, Martin A. 2007. Health care expenditures associated with autism spectrum disorders. Arch Pediatr Adolesc Med 161:350–355; doi:10.1001/archpedi.161.4.350.

Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 111:455–460; doi:10.1289/ehp.6000.

Libbey JE, Sweeten TL, McMahon WM, Fujinami RS. 2005. Autistic disorder and viral infections. J Neurovirol 11:1–10; doi:10.1080/13550280590900553.

Lipsitch M, Tchetgen Tchetgen E, Cohen T. 2010. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 21:383–8; doi:10.1097/EDE.0b013e3181d61eeb.

Lord C, Rutter M, Couteur A. 1994. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.

Lyall K, Pauls DL, Spiegelman D, Santangelo SL, Ascherio A. 2012. Fertility therapies, infertility and autism spectrum disorders in the Nurses' Health Study II. Paediatr Perinat Epidemiol 26:361–372; doi:10.1111/j.1365-3016.2012.01294.x.

Mandell DS, Cao J, Ittenbach R, Pinto-Martin J. 2006. Medicaid expenditures for children with autistic spectrum disorders: 1994 to 1999. J Autism Dev Disord 36:475–485; doi:10.1007/s10803-006-0088-z.

McFadden K, Minshew NJ. 2013. Evidence for dysregulation of axonal growth and guidance in the etiology of ASD. Front Hum Neurosci 7:671; doi:10.3389/fnhum.2013.00671.

MohanKumar SMJ, Campbell A, Block M, Veronesi B. 2008. Particulate matter, oxidative stress and neurotoxicity. Neurotoxicology 29:479–488; doi:10.1016/j.neuro.2007.12.004.

Napoli E, Wong S, Giulivi C. 2013. Evidence of reactive oxygen species-mediated damage to mitochondrial DNA in children with typical autism. Mol Autism 4:2; doi:10.1186/2040-2392-4-2.

Patterson PH. 2011. Maternal infection and immune involvement in autism. Trends Mol Med 17:389–394; doi:10.1016/j.molmed.2011.03.001.

Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, et al. 2009. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics 124:e195–e202; doi:10.1542/peds.2008-3506.

Quaak I, Brouns M, Van de Bor M. 2013. The dynamics of autism spectrum disorders: how neurotoxic compounds and neurotransmitters interact. Int J Environ Res Public Health 10:3384–3408; doi:10.3390/ijerph10083384.

Raz R, Lerner-Geva L, Leon O, Chodick G, Gabis LV. 2013. A survey of out-of-pocket expenditures for children with autism spectrum disorder in Israel. J Autism Dev Disord 43(10):2295–2302; doi:10.1007/s10803-013-1782-2.

Rice D, Barone S Jr. 2000. Critical periods of

vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 108:511–533.

Roberts AL, Kristen L, Hart JE, Laden F, Just AC, Bobb JF, et al. 2013. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. Environ Health Perspect 121:978–984; doi:10.1289/ehp.1206187.

Rodier PM. 1995. Developing brain as a target of toxicity. Environ Health Perspect 103(suppl 6):73–76.

Shimabukuro TT, Grosse SD, Rice C. 2008. Medical expenditures for children with an autism spectrum disorder in a privately insured population. J Autism Dev Disord 38:546–552; doi:10.1007/s10803-007-0424-y.

Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, et al. 1997. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 278:1078–1083.

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. 2008. Environmental exposures and adverse pregnancy outcomes: a review of the science. Reprod Sci 15:631–650; doi:10.1177/1933719108322436.

Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, et al. 2014. Patches of disorganization in the neocortex of children with autism. N Engl J Med 370:1209–1219; doi:10.1056/NEJMoa1307491.

Su JG, Jerrett M, Beckerman B, Wilhelm M, Ghosh JK, Ritz B. 2009. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ Res 109:657–670; doi:10.1016/j.envres.2009.06.001.

Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. 2008. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol 167:280–286; doi:10.1093/aje/kwm308.

Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S. 2011. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature 474:380–384; doi:10.1038/nature10110.

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. 2011. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect 119:873–877; doi:10.1289/ehp.1002835.

Volk HE, Lurmann F, Penfold B, Hertz-Piccotto I, McConnell R. 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 70:71–77; doi:10.1001/jamapsychiatry.2013.266.

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. 2006. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay Area. Environ Health Perspect 114:1438–1444; doi:10.1289/ehp.9120.

Yanosky JD, Paciorek CJ, Laden F, Hart JE, Puett RC, Liao D, et al. 2014. Spatio-temporal modeling of particulate air pollution in the conterminous United States using geographic and meteorological predictors. Environ Health 13:63; doi:10.1186/1476-069X-13-63.

Yanosky JD, Paciorek CJ, Schwartz J, Laden F, Puett R, Suh HH. 2008. Spatio-temporal modeling of chronic PM_{10} exposure for the Nurses' Health Study. Atmos Env (1994) 42:4047–4062; doi:10.1016/j.atmosenv.2008.01.044.

Yanosky JD, Paciorek CJ, Suh HH. 2009. Predicting chronic fine and coarse particulate exposures using spatiotemporal models for the Northeastern and Midwestern United States. Environ Health Perspect 117:522–529; doi:10.1289/ehp.11692.

A Section 508–conformant HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1409014.

Predictors of Indoor Radon Concentrations in Pennsylvania, 1989–2013

Joan A. Casey,[1] Elizabeth L. Ogburn,[2] Sara G. Rasmussen,[1] Jennifer K. Irving,[3] Jonathan Pollak,[1] Paul A. Locke,[1,4] and Brian S. Schwartz[1,3,5]

[1]Department of Environmental Health Sciences, and [2]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [3]Center for Health Research, Geisinger Health System, Danville, Pennsylvania, USA; [4]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [5]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Background: Radon is the second-leading cause of lung cancer worldwide. Most indoor exposure occurs by diffusion of soil gas. Radon is also found in well water, natural gas, and ambient air. Pennsylvania has high indoor radon concentrations; buildings are often tested during real estate transactions, with results reported to the Department of Environmental Protection (PADEP).

Objectives: We evaluated predictors of indoor radon concentrations.

Methods: Using first-floor and basement indoor radon results reported to the PADEP between 1987 and 2013, we evaluated associations of radon concentrations (natural log transformed) with geology, water source, building characteristics, season, weather, community socioeconomic status, community type, and unconventional natural gas development measures based on drilled and producing wells.

Results: Primary analysis included 866,735 first measurements by building, with the large majority from homes. The geologic rock layer on which the building sat was strongly associated with radon concentration (e.g., Axemann Formation, median = 365 Bq/m^3, IQR = 167–679 vs. Stockton Formation, median = 93 Bq/m^3, IQR = 52–178). In adjusted analysis, buildings using well water had 21% higher concentrations (β = 0.191, 95% CI: 0.184, 0.198). Buildings in cities (vs. townships) had lower concentrations (β = –0.323, 95% CI: –0.333, –0.314). When we included multiple tests per building, concentrations declined with repeated measurements over time. Between 2005 and 2013, 7,469 unconventional wells were drilled in Pennsylvania. Basement radon concentrations fluctuated between 1987 and 2003, but began an upward trend from 2004 to 2012 in all county categories ($p < 0.001$), with higher levels in counties having ≥ 100 drilled wells versus counties with none, and with highest levels in the Reading Prong.

Conclusions: Geologic unit, well water, community, weather, and unconventional natural gas development were associated with indoor radon concentrations. Future studies should include direct environmental measurement of radon, as well as building features unavailable for this analysis.

Citation: Casey JA, Ogburn EL, Rasmussen SG, Irving JK, Pollak J, Locke PA, Schwartz BS. 2015. Predictors of indoor radon concentrations in Pennsylvania, 1989–2013. Environ Health Perspect 123:1130–1137; http://dx.doi.org/10.1289/ehp.1409014

Introduction

Exposure to radon-222—an inert, odorless, and carcinogenic gas—is the second leading cause of lung cancer worldwide (Darby et al. 2005; Pawel and Puskin 2004). The U.S. Environmental Protection Agency (EPA) estimates that indoor radon exposure causes or contributes to about 21,000 lung cancer deaths in the United States annually (Pawel and Puskin 2004). In 1986, the U.S. EPA set an action level of 148 Bq/m^3 (4 pCi/L; there are 37 Bq/m^3 per pCi/L) based on the current state of radon testing and mitigation technologies [National Research Council (NRC) 1999a; U.S. EPA 1992].

Uranium-238 occurs naturally in soil and bedrock and decays to radium-226, which decays to radon. Both uranium-238 and radium-226 persist in the environment (half-lives of 4.5 billion years and 1,600 years, respectively). Radon-222 has a half-life of 3.8 days, and its radioactive decay products are responsible for its carcinogenicity. Pressure differentials between soil gas and indoor air cause the migration of radon through cracks and other openings into buildings, the primary source of indoor radon. Radium and radon are soluble in water, with concentrations increasing as salinity increases (Warner et al. 2012).

Several counties in eastern Pennsylvania overlie the Reading Prong, a physiographic section known to have high bedrock uranium concentrations (Gundersen 1991) and elevated indoor radon levels. The entire state has had some of the highest indoor radon levels in the United States. The Pennsylvania Department of Environmental Protection (PADEP) established a Radon Division that administers a program of radon monitoring and remediation (http://www.portal.state.pa.us/portal/server.pt/community/radon_division/21923).

U.S. Geological Survey (USGS) analysis of 548,547 indoor and short-term radon test results compiled by the PADEP during 1990–2007 reported that 39% of radon tests exceeded the U.S. EPA action level and that concentrations varied dramatically by geologic unit, a rock layer of a given lithology and geologic period (e.g., Annville Formation, high-calcium limestone from the Ordovician period) (Gross 2013). Geologists have identified 195 geologic units in Pennsylvania. Other factors that have been associated with higher indoor radon levels include the use of radon-rich well water [Folger et al. 1994; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2009], colder months, less precipitation, more expensive housing, rural area, and higher individual socioeconomic status (SES) (Cohen and Gromicko 1988; Folger et al. 1994; UNSCEAR 2009). Radon is present in natural gas used for cooking and heating; calculations performed in the 1970s suggested that it would not be expected to result in an increase in indoor radon levels (Johnson et al. 1973). Radon can also enter buildings from ambient air; however, outdoor radon concentrations are generally low, around 10 Bq/m^3, but can range from 1 to 100 Bq/m^3 (UNSCEAR 2009).

The development of unconventional natural gas in the Marcellus shale in Pennsylvania has the potential to exacerbate several pathways for entry of radon into buildings. The USGS reported 91,020 Bq/m^3 (n = 14) as the median radium concentration in produced water from Marcellus wells (Rowan et al. 2011), a value nearly 500 times the federal drinking water limit (185 Bq/m^3) and one that far exceeds the industrial discharge limit of 2,220 Bq/m^3. Underground, radon collects

Address correspondence to B.S. Schwartz, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Room W7041, Baltimore, MD 21205 USA. Telephone: (410) 955-4158. E-mail: bschwar1@jhu.edu

Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1409014).

We thank R.K. Lewis at the Pennsylvania Department of Environmental Protection, who facilitated the acquisition of the radon data. We also thank J.M. Crisp, who assisted with the assembling and cleaning of the Marcellus well data, and R.D. Peng, who provided statistical support.

This research was supported in part by the National Institutes of Health (grant R21 ES023675).

The authors declare they have no actual or potential competing financial interests.

Received: 30 July 2014; Accepted: 31 March 2015; Advance Publication: 9 April 2015; Final Publication: 1 November 2015.

in porous geological formations and thus in natural gas production wells (Gogolak 1980). Shales also tend to contain both higher concentrations of uranium (3.7–40 ppm) than other geologic formations and higher concentrations of radon in their natural gas (Gogolak 1980). The USGS reported preliminary data from 11 wellheads in Pennsylvania with corrected concentrations of radon (devices were calibrated for air measurement, but used in natural gas with correction factor = gas measurement × 1.47) ranging from 37 to 2,923 Bq/m^3 (median = 1,369) (Rowan and Kraemer 2012), suggesting that shale gas may have higher radon levels than other natural gas sources.

To our knowledge, no prior studies have evaluated predictors of radon concentrations in Pennsylvania. Our main objective was to identify the independent contribution to indoor radon concentrations of geologic unit, water source, building characteristics, season, weather, community SES, community type, and Marcellus shale development.

Methods

Study design. We obtained radon data on 1,983,705 indoor radon tests conducted in 806,469 buildings between 1987 and 2013 from all 67 counties in Pennsylvania; these tests were submitted by certified testers, laboratories, or homeowners to the PADEP Bureau of Radiation Protection, Radon Division. Buildings are most often tested during real estate transactions (World Health Organization 2009), and the PADEP requires reporting of all test results to their GreenPort website (http://www.depgreenport.state.pa.us/). We used the subset of radon measurements taken between 1 January 1989 and 31 December 2013 in our analysis because few samples were available from earlier years (n = 4,294) (Figure 1). The Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health reviewed the study protocol and did not consider it to be human subjects research.

Outcome: indoor radon concentration. Data included the address of the tested building, building type (12 types; Table 1), test location (i.e., basement, first floor, second floor), test type (i.e., activated charcoal, alpha-track detectors, charcoal liquid scintillation, continuous radon monitors, electret ion chamber), test dates, and radon concentration (Bq/m^3). Results were available for both short-term (2–7 days) and long-term (up to 1 year) testing periods. We used ArcGIS (version 10.0; Esri) and 10 street maps [e.g., TeleAtlas (TomTom), TIGER files (https://www.census.gov/geo/maps-data/data/tiger.html), and StreetMap Premium (Esri) from 2000–2012] to obtain latitude and longitude of buildings.

We excluded tests from buildings that could not be geocoded to an address, that were out of state, that were not taken on the first floor or basement, or that appeared in the database more than once (n = 394,008 buildings). Many buildings (n = 307,245) had multiple radon measurements (range, 2–56) taken on the same floor and day. For example, in buildings with two measurements per floor (n = 291,098), the correlation of floor-specific measurements was very high (ρ = 0.91). Because we had no information on building remediation, our primary analysis included only measurements taken during the first test day at each building (n = 866,735, including 224,666 averaged concentrations from the same floor and day). In a sensitivity analysis, we included up to four tests over time from each building.

Data sources. We obtained data on the public water service areas compiled by the PADEP from the Pennsylvania State University's Spatial Data Access website (Pennsylvania Spatial Data Access; http://www.pasda.psu.edu). Any home outside the public water supplier's service area was assumed to use well water. Statewide bedrock geology and physiographic sections were downloaded as shapefiles from the Pennsylvania Department of Conservation and Natural Resources (PADCNR; http://www.dcnr.state.pa.us). On average, each geologic unit covers 749 noncontiguous square kilometers. One important geologic unit is the felsic gneiss, which is found throughout the state. The Reading Prong section primarily contains felsic gneiss; however, the section is present in only three counties, identified as Reading Prong counties in Figure 2.

We downloaded monthly average temperature and rainfall in 10 regions from the Pennsylvania State Climatologist (http://climate.psu.edu). Based on 2000 U.S. Census boundary files, buildings were assigned to a minor civil division: cities, moderate- to high-density boroughs, and suburban and

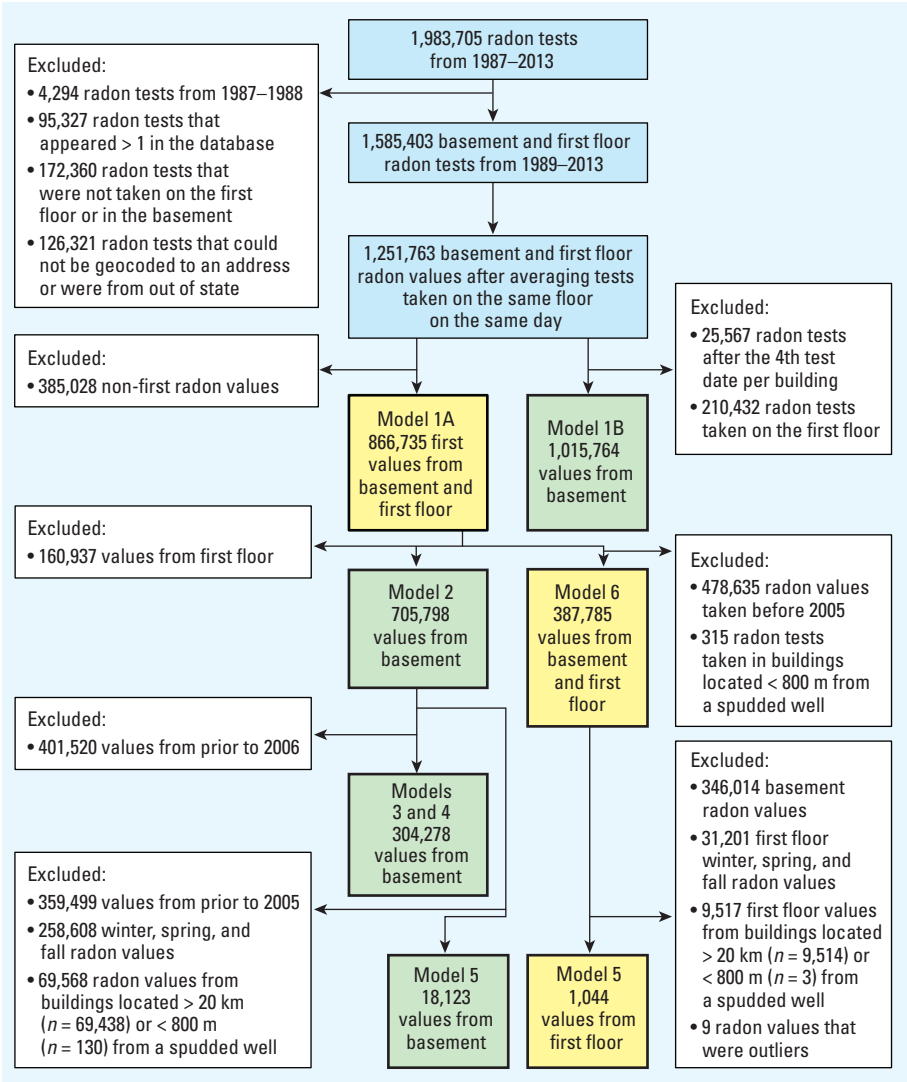


Figure 1. Flow diagram of radon tests included in six primary models.

Table 1. Radon concentrations (Bq/m^3) by test and building characteristics, stratified by test location.

Variable	Category	Basement*			First floor*		
		n (%)	Median (IQR)	Range	*n* (%)	Median (IQR)	Range
All results	Total	705,798 (100)	118.4 (59.2–262.7)	0–69,057	160,937 (100)	55.5 (29.6–111.0)	0–111,481
U.S. EPA action level	< 148 Bq/m^3	408,184 (57.8)	66.6 (40.7–99.9)	0–147.9	131,245 (81.6)	44.4 (25.9–74)	0–147.9
	≥ 148 Bq/m^3	297,614 (42.2)	310.8 (207.2–580.9)	148–69,057	29,692 (18.5)	262.7 (188.7–447.7)	148–111,481
Well water use	No	591,565 (83.8)	111.0 (58.1–236.8)	0–69,057	138,804 (86.3)	51.8 (27.8–103.6)	0–111,481
	Yes	114,233 (16.2)	185.0 (81.4–458.8)	0–55,463	22,133 (13.8)	74.0 (37.0–164.7)	0–14,822
Building type	2-Story	298,672 (42.3)	114.7 (61.1–114.7)	0–55,463	73,340 (45.6)	53.65 (29.6–103.6)	0–111,481
	3-Story	69,008 (9.8)	166.5 (77.6–166.5)	2.2–33,973	8,837 (5.5)	70.3 (33.3–162.8)	0.7–7,478
	Apartment	1,999 (0.3)	82.0 (44.4–173.9)	3.7–5,254	1,042 (0.7)	33.3 (18.5–68.5)	0.7–1,395
	Bi-level	12,599 (1.8)	131.3 (62.9–294.2)	1.1–25,937	2,628 (1.6)	77.7 (37.0–166.5)	1.9–9,476
	Cape Cod	15,801 (2.2)	127.7 (70.3–257.2)	0–29,637	3,837 (2.4)	59.2 (29.6–103.6)	0–29,711
	Commercial	1,773 (0.3)	77.7 (42.6–157.3)	3.7–4,449	871 (0.5)	40.7 (22.2–83.9)	0.7–6,915
	Contemporary	4,156 (0.6)	136.0 (66.6–296)	3.7–25,530	1,968 (1.2)	51.8 (25.9–108.8)	3.7–2,760
	Public/school	370 (0.1)	94.7 (47.2–203.5)	13.6–5,176	202 (0.1)	51.8 (27.1–96.2)	3.7–636
	Ranch	63,946 (9.1)	151.7 (79.6–323.2)	0.9–69,057	14,764 (9.2)	66.6 (37.0–136.9)	0–10,286
	Split level	17,788 (2.5)	107.3 (59.2–218.3)	1.5–41,607	5,822 (3.6)	59.2 (33.3–107.3)	0–8,251
	Townhouse	42,691 (6.1)	68.5 (40.7–125.8)	0.2–32,751	16,920 (10.5)	37.0 (22.2–66.6)	0–22,459
	Trailer	183 (0.03)	88.8 (51.8–192.4)	18.5–2,531	139 (0.1)	33.3 (18.5–33.3)	3.7–662
	Unknown	176,812 (25.1)	122.1 (55.5–297.9)	0–35,668	30,567 (19.0)	62.9 (29.6–153.0)	0–16,119
Test type	Activated charcoal	237,932 (33.7)	129.5 (55.5–325.6)	0–69,057	54,957 (34.2)	59.2 (25.9–142.5)	0–50,294
	Alpha track	7,074 (1.0)	161.1 (81.4–333.0)	0.7–14,796	1,844 (1.2)	99.9 (42.7–221.4)	0.4–3,441
	Charcoal liquid scintillation	44,936 (6.4)	162.8 (70.3–392.2)	0–32,751	4,934 (3.1)	77.7 (33.3–186.9)	3.7–16,119
	Continuous	209,994 (29.8)	114.7 (59.2–236.8)	0.2–41,544	14,647 (9.1)	48.1 (25.9–92.5)	0.1–111,481
	Electret ion chamber	205,862 (29.2)	111.0 (62.9–214.6)	0–62,974	84,555 (52.5)	53.65 (29.6–99.9)	0–29,711
Test duration	1–7 days	693,864 (98.3)	118.4 (59.2–262.7)	0–69,057	157,912 (98.2)	55.5 (29.6–111.0)	0–111,481
	≥ 8 days	11,934 (1.7)	148.0 (74.0–310.8)	0–69,057	3,025 (1.8)	81.4 (37.0–181.3)	0–3,593
Season	Winter	169,921 (24.1)	114.7 (59.2–247.9)	0–55,463	37,886 (23.5)	48.1 (25.9–96.2)	0–50,294
	Spring	198,485 (28.1)	114.7 (59.2–229.4)	0–62,974	46,432 (28.9)	51.8 (27.8–98.1)	0–22,496
	Summer	174,007 (24.7)	133.2 (66.6–299.7)	0–41543.6	40,320 (25.1)	66.6 (33.3–136.9)	0–111,481
	Autumn	163,385 (23.2)	118.4 (59.2–292.3)	0–69,057	36,886 (22.6)	59.2 (29.2–129.5)	0–29,711
Average temperature in month of test (°C)	< 0	84,259 (11.9)	3.3 (1.6–8.0)	0.004–930	17,294 (10.8)	1.6 (0.8–3.7)	0–276
	0 to < 10	232,372 (32.9)	3.3 (1.6–7.7)	0–1,866	53,651 (33.3)	1.6 (0.8–3.4)	0–3,013
	10 to < 18.3	189,693 (26.9)	3.4 (1.7–7.3)	0–1,499	43,018 (26.7)	1.5 (0.8–3.0)	0–607
	≥ 18.3	199,474 (28.3)	3.0 (1.6–6.2)	0–1,702	46,974 (29.2)	1.4 (0.7–2.6)	0–608
Average rainfall in month of test (cm)	< 7.1	236,239	125.8 (62.9–281.9)	0–69,056	53,693	59.2 (29.6–121.0)	0–50,294
	7.2–10.8	232,866	116.6 (59.2–251.6)	0–62,974	55,928	55.5 (29.6–107.3)	0–111,481
	≥ 10.9	236,693	116.6 (59.2–255.3)	0–41,607	51,316	53.7 (27.8–107.3)	0–22,496
Community socioeconomic deprivation quartile[a]	1 (< –4.9)	169,327 (24.5)	118.4 (59.2–262.7)	0–35,897	46,100 (29.4)	59.2 (29.6–118.4)	0–50,294
	2 (–4.9 to –3.3)	172,068 (24.9)	133.2 (66.6–306.0)	0–55,463	37,389 (23.8)	62.9 (33.3–129.5)	0–29,711
	3 (–3.2 to –1.1)	177,619 (25.7)	129.5 (66.6–284.9)	0–69,057	36,734 (23.4)	59.2 (29.6–114.7)	0–18,537
	4 (≥ –1.0)	173,407 (25.0)	103.6 (53.7–222.0)	0–35,668	36,742 (23.4)	44.4 (24.1–92.5)	0–111,481
Minor civil division	Township	488,168 (69.2)	130.7 (64.8–299.7)	0–55,463	116,311 (72.3)	59.2 (29.6–122.1)	0–50,294
	Borough	133,990 (19.0)	112.9 (59.2–233.1)	0–69,057	25,643 (15.9)	51.8 (25.9–103.6)	0–22,496
	City	83,638 (11.9)	79.6 (44.4–148.0)	0–31,361	18,983 (11.8)	40.7 (22.2–70.7)	0–111,481
County category[b]							
No Marcellus activity	Other counties	379,223 (53.7)	120.3 (59.2–273.8)	0–62,974	112,252 (69.8)	55.5 (29.6–111.0)	0–50,294
Low Marcellus activity	< 100 drilled wells by 2013	174,216 (24.7)	114.7 (62.9–233.1)	0–30,621	22,734 (14.1)	55.5 (27.4–118.4)	0–22,496
High Marcellus activity	≥ 100 drilled wells by 2013	57,814 (8.2)	129.5 (70.3–260.9)	0–30,858	5,753 (3.6)	62.9 (33.3–129.5)	2.6–111,481
Reading Prong	Berks, Lehigh, and Northampton	62,635 (8.9)	192.4 (85.1–425.5)	0–69,057	9,632 (6.0)	96.2 (44.4–210.9)	0–14,822
Philadelphia	Philadelphia	31,910 (4.5)	62.9 (37.0–105.5)	0–31,361	10,566 (6.6)	37.0 (22.2–62.9)	0–2,331
Drilled well within 20 km of building	No	637,317 (90.3)	118.4 (59.2–266.4)	0–69,057	156,731 (97.4)	55.5 (29.6–111.0)	0–50,294
	Yes	68,481 (9.7)	124.0 (70.3–244.2)	0–38,658	4,206 (2.6)	59.2 (33.3–120.3)	3.7–111,481
Drilled-well exposure quartile[c]							
1	< 0.19 well/km^2	17,086 (25.0)	120.3 (70.3–225.7)	3.7–23,465	1,086 (25.8)	70.3 (37.0–133.2)	3.7–2,742
2	0.19 to 0.61 well/km^2	17,099 (25.0)	125.8 (70.3–255.3)	18.5–29,637	1,073 (25.5)	59.2 (29.6–114.7)	18.5–8,251
3	0.62 to 1.4 well/km^2	17,126 (25.0)	125.8 (70.3–247.9)	18.5–30,858	1,046 (24.9)	55.5 (29.6–107.3)	14.8–3,559
4	> 1.4 well/km^2	17,170 (25.1)	125.8 (70.3–247.9)	18.5–19,769	1,001 (23.8)	59.2 (37.0–122.1)	18.5–111,481
Producing-well exposure quartile[d]							
1	< 2.55 m^3/day/km^2	83,971 (24.3)	111.0 (55.5–247.9)	2.6–40,928	13,052 (31.2)	51.8 (26.3–99.9)	0–8,131
2	2.55 to 294.4 m^3/day/km^2	86,196 (24.9)	120.3 (61.1–266.4)	7.4–35,897	10,826 (25.9)	59.2 (30.9–118.4)	0–29,711
3	294.5 to 4312.6 m^3/day/km^2	86,989 (25.1)	125.8 (62.9–281.2)	11.1–62,974	10,034 (24.0)	59.2 (33.3–122.1)	3.7–12,119
4	> 4312.7 m^3/day/km^2	89,143 (25.7)	133.2 (70.3–288.6)	11.1–30,858	7,879 (18.9)	61.1 (33.3–124.0)	5.6–111,481

[a]Not available for buildings located in Philadelphia or Pittsburgh. Community socioeconomic deprivation was assigned at the township, borough, or census-tract level, based on six indicators derived from the 2000 U.S. Census: combined less than high school education, not in the labor force, in poverty, on public assistance, civilian unemployment, and does not own a car; a higher score represents a more deprived community. [b]No Marcellus activity (other counties): Adams, Bedford, Bucks, Carbon, Chester, Cumberland, Dauphin, Delaware, Erie, Franklin, Fulton, Juniata, Lancaster, Lebanon, Mifflin, Montgomery, Montour, Northumberland, Perry, Pike, Schuylkill, Snyder, Union, and York; low Marcellus activity counties: Allegany, Beaver, Blair, Cambria, Cameron, Centre, Clarion, Columbia, Crawford, Elk, Forest, Huntingdon, Indiana, Jefferson, Lackawanna, Lawrence, Luzerne, McKean, Mercer, Potter, Somerset, Sullivan, Venango, Warren, and Wayne; high Marcellus activity counties: Armstrong, Bradford, Butler, Clinton, Clearfield, Fayette, Greene, Lycoming, Susquehanna, Tioga, Washington, Westmoreland, and Wyoming. [c]Restricted to 2005–2013 and buildings within 20 km of a drilled well at the time of the radon test. [d]Restricted to 2005–2013. *Categories of all variables shown had statistically significantly different ln-radon concentrations by ANOVA.

rural townships. Community socioeconomic deprivation, an indicator of community SES, was derived from six *z*-transformed U.S. Census 2000 variables (Schwartz et al. 2011). Marcellus shale development data covering 1 January 2005 through 31 December 2013, came from PADEP and PADCNR, with the latitude and longitude of each well, the date of well drilling, natural gas produced, and number of producing days.

Marcellus shale development metrics. The Marcellus Formation is 1,500–2,500 m underground and underlies a large section of Pennsylvania from the southwest curling northeast. Only unconventional wells (horizontal wells, hydraulic fracturing) were included (Figures 2 and 3).

The spud date was the day well drilling began, and the production start date was the day the well first produced natural gas. We estimated a start date of production for each well:

$$\text{Production start date at well } i = (l_p - k_p)I_p, \quad [1]$$

where l_p is the last day of production in period p, k_p is the number of days in production in period p, and I_p equals 1 when period p is the first period of production for well i, and 0 otherwise. We estimated daily natural gas production for each well in its first production period as the volume of gas produced in its first period divided by the number of days of reported production. In subsequent periods we estimated daily gas production as the volume of gas reported in each period, divided by the number of days in that production period. When wells were missing one or more production volumes by period, we imputed missing volumes for periods in which there were data before and after (n = 102 wells), assuming a linear decline over time. We imputed missing spud dates (n = 149 wells) using conditional mean imputation based on production start date, stimulation (hydraulic fracturing) date, year, and geographic region.

Two primary Marcellus development metrics were created based on all wells in the state, one on drilled wells and the other on wells in production. Wells drilled prior to the start of an indoor radon test were included in that building's exposure assignment. Once a well was drilled, it was assumed to contribute until the end of the study period, 31 December 2013. We calculated drilled-well exposure assignment:

$$\text{Building } j \text{ metric} = \Sigma_{i=1}^{n}\Sigma_{k=1}^{l}(I_A(k,m)/d_{ij}^2)/m, \quad [2]$$

where n is the number of drilled wells, m is the duration of the indoor radon test in days, k is the day with 1 equal to 1 January 2005, and l is equal to 3,287 (to 31 December 2013), $I_A(k,m)$ is 1 when well i has been drilled before day k and the indoor radon test at building j is conducted from day k to day $k + m$, and 0 otherwise, and d_{ij}^2 is the squared-distance between the coordinates of the wellhead of well i and building j. We calculated the producing-well exposure assignment:

$$\text{Building } j \text{ metric} = \Sigma_{i=1}^{n}\Sigma_{k=1}^{l}(I_A(k,m)g_p/d_{ij}^2)/m, \quad [3]$$

where n is the number of producing wells, m is the duration of the indoor radon test in days, k is the day with 1 equal to 1 January 2005 and l is equal to 3,287 (to 31 December 2013), $I_A(k,m)$ is 1 when well i is producing on day k and the indoor radon test at building j is conducted from day k to day $k + m$, and 0 otherwise, g_p is the estimated amount of natural gas produced (in thousands of cubic meters) by well i on day k, and d_{ij}^2 is the squared distance between the coordinates of the wellhead of well i and building j.

Statistical analysis. The goal of the analysis was to evaluate associations of year, county category, geologic unit, community type, community SES, well water use, and metrics of unconventional natural gas development with indoor radon concentrations. Building was the unit of analysis. The distribution of radon concentrations was skewed, so we used natural log-transformed radon concentration (ln-radon) as our outcome variable to improve compliance with assumptions of linear regression (i.e., homoscedasticity and normality of residuals). We used one-way analysis of variance (ANOVA) to assess unadjusted differences in indoor radon concentrations by other covariates. To evaluate associations with indoor ln-radon concentration, we used multivariable linear regression and generalized estimating equations to account for within-building correlation when models included more than one measurement per building. When beta coefficients are < 0.1, 100 × β can be interpreted as approximating the percent change in radon concentration associated with a 1-unit change in the independent variable. In models used to assess the spatial distribution of radon levels, we wanted to remove the contribution of building-related factors. Models used to assess associations of unconventional natural gas development with

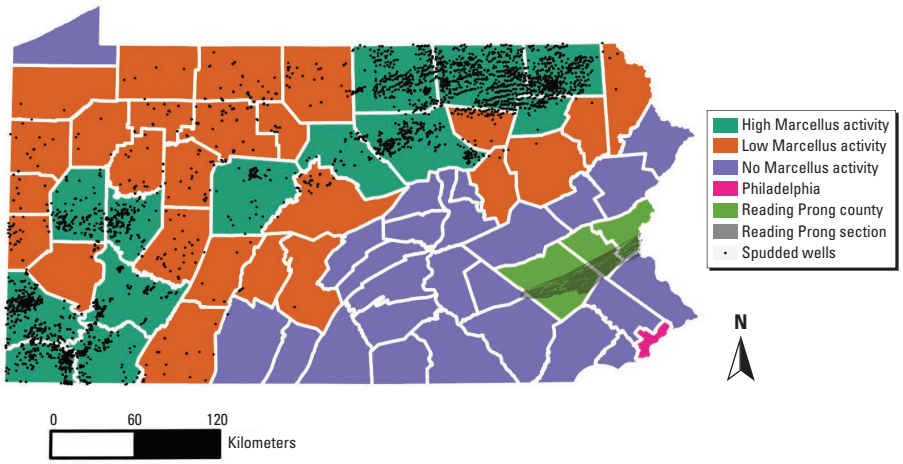


Figure 2. County category groupings, the Reading Prong section, and location of spudded Marcellus wells (through 2013).

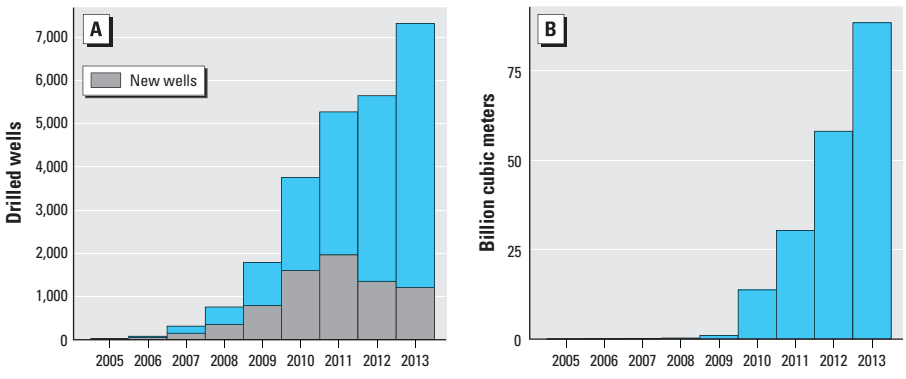


Figure 3. (*A*) Number of new unconventional wells drilled annually during 2005–2013 (gray) and cumulative number of wells. (*B*) Unconventional natural gas produced (billions of cubic meters) during 2005–2013.

radon levels did not contain county, minor civil division, or community SES because of concern about overadjustment. Covariates were included in models 1–4 because of *a priori* hypotheses that they could confound the relationship between our primary variables of interest and ln-radon concentration or based on the quasi-likelihood information criterion (Hardin and Hilbe 2013).

Model 1A included only measurements taken on the first test date at each building (n = 762,725 buildings and n = 866,735 radon values), which included some averaged values when multiple tests were performed on the same floor on the same day. Model 1A was adjusted for test year (1989–2013), test location (basement or first floor), well water use (yes or no), 13 building types (including "unknown"), test type (listed above), test duration, season, weather (average temperature and rainfall for 10 regions during the month radon measurement began with linear, quadratic, and cubic terms to account for nonlinearity), minor civil division, county (n = 67), and 179 mutually exclusive geologic units [reference group = Stockton Formation (n = 62,026) plus 12 geologic units with < 20 tests]. We used model 1B to evaluate changes over time in within-building basement radon levels by estimating model 1A, restricted to basement measurements, from up to four testing dates per building (n = 714,097 buildings and n = 1,015,764 radon values). We also assessed changes in radon levels over time for buildings with high initial concentrations by restricting model 1B to buildings with initial radon concentrations ≥ 740 Bq/m^3 (n = 55,161 buildings and n = 99,293 radon values).

In model 2, we assessed differential changes in basement radon concentration by place and time by removing county from model 1A and restricting to basement radon values (n = 705,798 buildings and radon values). We ran five separate regressions by county category [Philadelphia, Reading Prong (which have no Marcellus activity), low Marcellus activity (< 100 wells drilled by 2014), high Marcellus activity (≥ 100 wells drilled by 2014), and no Marcellus activity] (see Supplemental Material, Table S1). We then plotted the predicted values of the geometric mean radon concentration by county category and year; 95% confidence intervals (CIs) were estimated using the delta method (Cox 1998).

We produced two maps of statewide basement radon concentrations for 2006–2013. The first displayed median radon concentrations per geologic unit (with ≥ 10 measurements). In the second, we removed variability due to building-level factors (which could help target remediation efforts to certain locations). We did this with model 3 by regressing ln-radon on building-level factors (i.e., year, building type, test type, test duration, season, average temperature and rainfall). In model 4, we fit a linear regression of the residuals from model 3 on only geologic unit, county, and well water use (n = 304,278 buildings and radon values) and then used model 4 to output new predicted radon concentrations in a 500-m × 500-m grid statewide. Split samples suggested that model 4 predicted well, and residual semivariogram plots did not exhibit spatial autocorrelation.

We used models 5 and 6 to evaluate two *a priori* hypotheses of the possible contribution of unconventional natural gas development on indoor radon concentrations: *a*) Ambient air could contribute to indoor radon concentrations through the release of radon and radium in the drilling process, primarily in the summer when buildings are more likely to be open; and *b*) produced natural gas containing radon could enter building air through use of natural gas for cooking or unvented heating and, given a transit speed of about 16 km/hr in pipelines (Gogolak 1980), all buildings in the state could be affected.

In model 5, we evaluated the associations of the drilled well metric (Equation 2) with ln-radon concentration by restricting model 1A to the years 2005–2013 (primary years of Marcellus development); measurements taken only during July, August, and September; and buildings located within 20 km of a drilled well at the time of the radon test. Because summer months had little variability in temperature, we did not include temperature in model 5. We also fit model 5 separately for first floor (n = 1,044 buildings and radon values) and basement (n = 18,123 buildings and radon values) because of hypotheses about pathways of radon entry. Model 5 excluded 3 first-floor and 130 basement radon concentrations from buildings located within 800 m of a well because we did not have enough data to fit a curve for distances < 800 m and 9 first-floor radon values that were outliers (studentized residuals > 3). As a counterfactual analysis, we re-ran model 5 including buildings from 1989 through 2005 that would be located within 20 km of a Marcellus well by December 2013.

To evaluate associations of the producing-well metric (Equation 3) and ln-radon concentrations, in model 6, we restricted model 1A to the years 2005–2013 and excluded buildings located within 800 m of a producing well (n = 315). Because year and the production well metric were highly correlated (ρ = 0.95), the regression models could not separate their independent influence; therefore, we presented model 6 production associations as unadjusted and adjusted for year, as well as year associations unadjusted for production. Regression analysis was performed using Stata 13 (StataCorp). We tested for linear trend by year by including year as a continuous variable. Alpha was set at 95%, and statistical significance was $p < 0.05$. Exposure metric creation and radon predictions were performed using R, version 3.0.0 (R Core Team 2013) and the sp package.

Results

Our primary analysis included 866,735 first indoor radon values from 762,725 buildings collected during 1989–2013. Every county reported results (see Supplemental Material, Table S2), with a median of 3,447 and ranging from 59 in Forest to 99,590 in Allegheny. Most (81.4%) of the values were from basements (n = 705,798), with a median concentration of 118.4 Bq/m^3 [interquartile range (IQR) = 59.2–262.7]; 42.2% of these values in basements (n = 297,614) met or exceeded the U.S. EPA action level (Table 1). Radon concentrations varied within and between county categories across the study period, with Reading Prong counties having significantly higher and Philadelphia significantly lower radon concentrations.

In total, 7,469 unconventional natural gas wells were drilled in 39 Pennsylvania counties during 2005–2013 (Figure 3A). More than 5,000 of those wells entered production, producing 191 billion m^3 of natural gas during 2009–2013 (Figure 3B). We identified 1,056 buildings with radon values from the first floor collected during the summer and located within 20 km of a drilled well at the time of the test. The median of the drilled well metric of these buildings was 0.6 wells/km^2 (IQR = 0.2–1.3). The median of the producing-well metric of buildings statewide was 294 m^3/day/km^2 (IQR = 3–4,464). There were increasing median radon concentrations across quartiles of the production well metric for both the first floor and basement (Table 1).

In unadjusted analysis, several variables were associated with indoor radon concentrations: well water, building type, duration of test, season, weather during the test, community SES, community type, and county; geologic unit associations were strong, with large variation by unit [e.g., Axemann Formation, median = 365 Bq/m^3 (IQR = 167–679), vs. Stockton Formation, median = 93 Bq/m^3 (IQR = 52–178); Table 1]. Communities with lower SES had lower radon levels, but this variable was not included in subsequent models because of concerns regarding mediation (i.e., drilling improves individual SES and community SES, but richer individuals have more tightly sealed homes and higher radon concentrations).

In adjusted analysis (model 1A, n = 866,735 first basement and first-floor values), many variables were associated

with radon concentrations. Strong associations were observed for specific geologies, for example Axemann, Bellefonte, and Nittany Formations were associated with 220–250% higher radon concentrations, compared with the Stockton Formation (see Supplemental Material, Table S2). Alpha track (generally long-term) and charcoal liquid scintillation tests were associated with 23% and 27% higher radon levels, respectively, compared with activated charcoal tests. Buildings using well water (vs. municipal water) also had 21% higher concentrations (β = 0.191; 95% CI: 0.184, 0.198). Buildings in cities versus townships were associated with lower radon levels (β = –0.323; 95% CI: –0.333, –0.314). There were nonlinear associations of rainfall and temperature; less rainfall and cooler temperatures were generally associated with higher radon concentrations. When up to four temporally ordered basement measurements per building were evaluated (model 1B, n = 1,015,764), we observed a significant decrease in radon concentration across tests, with a 37.1% (95% CI: 36.7, 37.3) decline from test 1 to test 2, 51.5% (95% CI: 51.1, 51.9) from test 1 to test 3, and 58.0% (95% CI: 57.4, 58.9) from test 1 to test 4 (see Supplemental Material, Table S3). Among buildings with an initial basement radon concentration ≥ 740 Bq/m^3, we observed from the first test an 88.8% (95% CI: 88.6, 88.9) decline to the second test, and a 92.3% (95% CI: 92.1, 92.4) decline to the third test (see Supplemental Material, Table S4).

After controlling for confounding variables including geologic unit (model 2, basement values only), there was evidence of an upward trend from 2004 to 2012 (p < 0.001). Confidence intervals overlapped among the high, low, and no Marcellus activity counties, particularly between no activity and high activity counties before 2004, whereas there was little or no overlap after that time, with high activity counties having the highest estimated radon concentrations, followed by no activity and low activity counties, respectively. However, fewer measurements were taken in earlier years, resulting in less precise estimates with more variation from year to year (Figure 4). It should be noted that when both basement and first-floor values were included (model 1A; see Supplemental Material, Table S2) the upward trend began in 2006 (p < 0.001). There were large differences across the state in median radon concentrations by geologic unit (Figure 5A). Geologic unit and well water use did not appear to make large contributions to indoor radon concentrations in regions with many drilled Marcellus wells (Figure 5B, models 3 and 4).

The drilled well metric was significantly associated with first-floor summer radon concentrations in buildings located within 20 km of a drilled well; for each additional drilled well per square kilometer surrounding the building, first-floor radon levels were estimated to be 2.8% higher (drilled well β = 0.028; 95% CI: 0.001, 0.05) (model 5). We also found a positive, but attenuated, association with basement measurements (drilled well β = 0.010; 95% CI: 0.003, 0.020). In a sensitivity analysis, there was no association between the counterfactual drilled well metric for future wells and summer first-floor concentrations between 1989 and 2005 (drilled well β = 0.001; 95% CI: –0.022, 0.024).

The producing-well metric was not associated with indoor radon concentration when year was included in model 6 (production β = –0.001; 95% CI: –0.003, 0.002); when year was not associated, gas production was significantly associated with indoor radon concentration and radon concentrations were estimated to be 1.3% higher with each additional 100 m^3 of natural gas produced per day per square kilometer (production β = 0.013; 95% CI: 0.005, 0.020). There was a positive association between year and radon concentrations between 2005 and 2013, when the production metric was removed

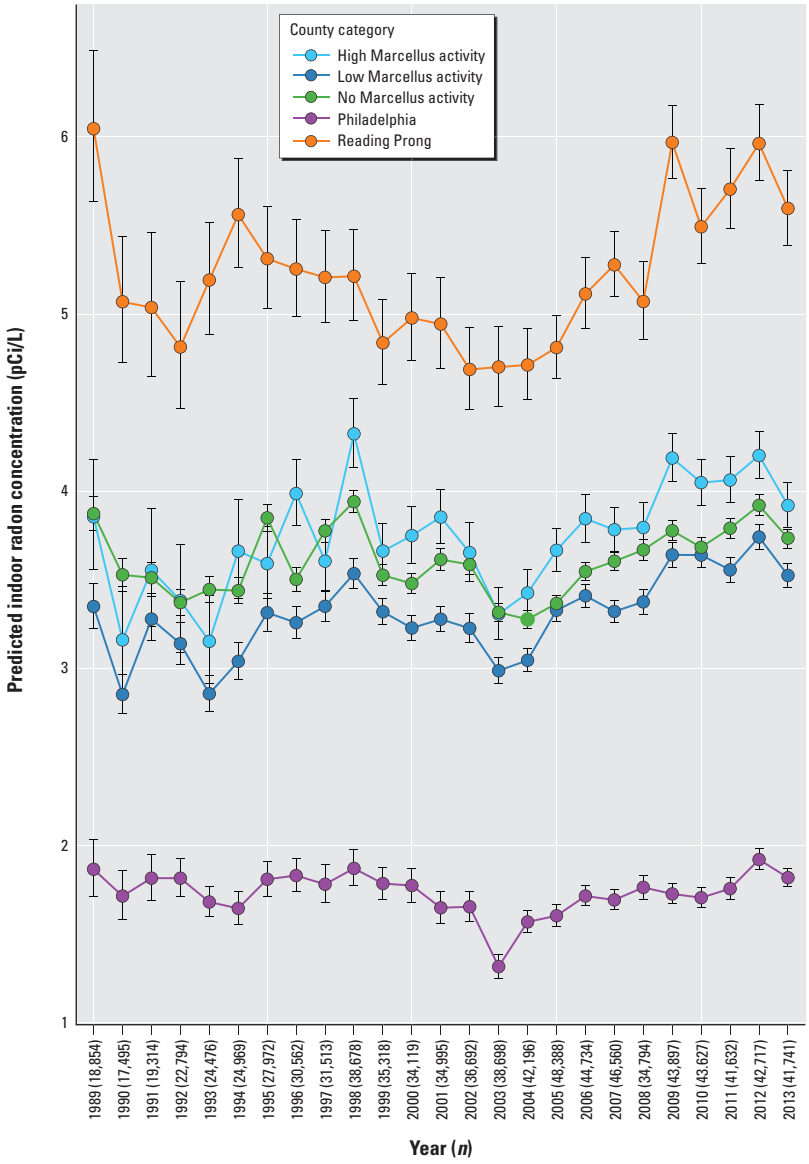


Figure 4. Geometric mean and 95% confidence intervals for indoor basement radon concentrations in five county categories, 1989–2013. High Marcellus shale counties had at least 100 unconventional wells drilled by 2013, and low Marcellus shale counties had 1–100. Predicted values were generated from five separate linear regression models (one for each county category) including only measurements taken on the first test date at each building (n = 705,798 values), adjusted for test year (1989–2013), well water use, 13 building types, five test types, test duration, season, weather (average temperature and rainfall with linear, quadratic, and cubic terms), minor civil division, and 179 mutually exclusive geologic units (model 2).

from model 6 (year β = 0.012; 95% CI: 0.011, 0.014).

Discussion

We identified several predictors of indoor radon concentrations in Pennsylvania, a state with historically high radon levels (Alter and Oswald 1987). Water source, building type, test type, test duration, season, weather, county, and geologic unit were associated with indoor radon concentration. When data were aggregated to county categories, on average, Reading Prong counties had the highest indoor radon concentrations (Table 1, Figure 4). Nearly 300,000 homes had a first basement test result that exceeded the U.S. EPA action level. We observed fluctuating radon concentrations throughout the study period; low Marcellus activity counties consistently had lower radon concentrations than either high or no Marcellus activity, before and after drilling began. From 2005 through 2013 the high activity counties had higher basement radon levels than either low or no Marcellus activity counties, with confidence intervals that did not overlap, and there was evidence of a significant upward trend (Figure 4). In a model using first-floor and basement values and adjusting for each county (model 1A), radon concentrations only began increasing in 2006 (see Supplemental Material, Table S2). When we included multiple basement measurements per building, radon levels declined with repeated measurements within a building, which is good news for public health and also suggests that state remediation programs are effective.

Buildings located in cities had nearly 27% lower radon levels than those located in more rural townships (Table 2; see also Supplemental Material, Table S2). Previous work suggests that this difference is not due to weatherization of homes (Cohen and Gromicko 1988); it may occur because cities are sited in low-lying, alluvial sites, where radon levels are low (Briggs et al. 2008). However, the association persisted after adjustment for geologic unit and community SES. Buildings located in poorer communities also tended to have lower radon concentrations, consistent with past research (Cohen and Gromicko 1988).

We found that buildings using well water had 21% higher indoor radon concentrations than those using municipal water. The release of waterborne radon during showering or washing can contribute to concentrations in buildings. The NRC has estimated that 10,000 pCi/L (37,000 Bq/m^3) of waterborne radon entering a building is needed to increase indoor air concentration by 1 pCi/L (37 Bq/m^3) (NRC 1999b). Our 20% increase represented approximately 37 Bq/m^3. An early study of Pennsylvania groundwater wells reported that only 10% exceeded 185,000 Bq/m^3 (Swistock et al. 1993), putting our estimate at odds with the rule of thumb.

We found a statistically significant association between proximity to unconventional natural gas wells drilled in the Marcellus shale and first-floor radon concentration in the summer, with a positive—but attenuated—association for basement levels, which suggests a pathway through outdoor ambient air but does not rule out the possibility of radon moving from the basement to the first floor. Geographic location did not appear to account for the association because we did not find an association in buildings prior to 2006 that would be located near Marcellus wells in the future. Prior studies suggest that levels of radon in ambient air are low; our finding merits further study because the Marcellus shale is known to contain elevated levels of uranium (U.S. EPA 2008), and flowback water and reserve pit soil can contain elevated levels of radium, which could create an environmental exposure pathway (Rich and Crosby 2013; Rowan et al. 2011; Warner et al. 2012). It is also possible that radon could enter buildings through the use of natural gas containing radon. However, concentrations at the wellhead in Pennsylvania have a median of 1,369 Bq/m^3 (Rowan and Kraemer 2012), much lower than the 37,000 Bq/m^3 thought needed to increase radon concentrations by 12.2 Bq/m^3 annually in homes that use gas appliances (Gogolak 1980). Our findings should be interpreted in the context of Pennsylvania's recent *Technologically Enhanced Naturally Occurring Radioactive Material (TENORM)* study report from January 2015, which concluded that

> There is little potential for additional radon exposure to the public due to the use of natural gas extracted from geologic formations in Pennsylvania. (Perma-Fix Environmental Services Inc. 2015)

However, the study did detect radon in several components of the unconventional natural gas development process and waste stream, such as natural gas, drill cuttings, and wastewater.

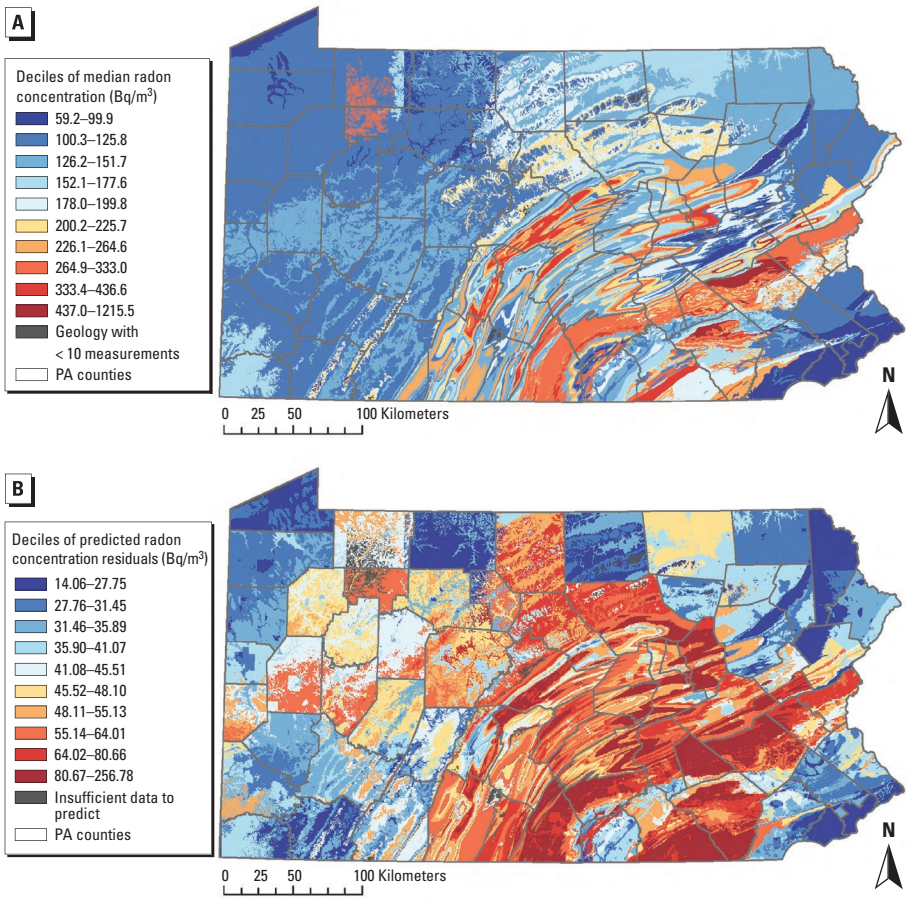


Figure 5. (*A*) Unadjusted median basement radon concentrations (*n* = 304,278 tests) in Pennsylvania by geologic unit during 2006–2013. (*B*) Predicted contribution to basement radon concentration from geologic unit, county, and well water after accounting for variation due to year (2006–2013), building type, test type, test duration, season, average temperature, and average rainfall (based on models 3–4; *n* = 304,278 values).

Our analysis had several limitations. We had no information on radon-resistant construction, construction year, types of remediation completed, type of heating and cooking systems, quantity of natural gas and water used in the building, degree of sealing of the building for energy efficiency, soil type near the building, wind speed and direction, or individual SES. These missing data make attributing increased radon levels to a particular source difficult. For instance, it is possible that the observed upward trend from 2004 to 2012 was simply the result of buildings being sealed more tightly during this time.

We did not know whether a radon professional or a homeowner performed each radon test. However, homes are usually tested during real estate transactions, and radon professionals generally perform these tests, ensuring impartial results. Tests are also performed when people are worried about their levels or want to retest after abatement. Worry about levels could introduce a form of selection bias sometimes observed in universal screening programs in which those with higher radon levels would be more likely to test first, which would account for the temporal trends up to 2005. We addressed the abatement concern by only including first measurements. In addition, our analysis should be considered exploratory because we did not perform any environmental radon measurements specifically directed at evaluating the Marcellus or well water hypotheses.

Conclusion

Radon continues to be a concern in Pennsylvania, and geology is an important contributor. Well water may contribute more to indoor radon than previously thought. There has also been a general rise in concentrations since 2006. The measurements of the Pennsylvania TENORM study should be periodically repeated given the projection of 60,000 wells in Pennsylvania by 2030 (Johnson 2010). Future studies of building radon levels should include more information about buildings, such as age, heating systems, remediation intervention, and radon-resistant construction. Radon exposure represents a major environmental health risk, and in addition to future studies to understand the impact of drilling on radon levels, there is continuing need for a radon program in Pennsylvania to track and evaluate radon concentrations and to encourage testing and remediation.

References

Alter HW, Oswald RA. 1987. Nationwide distribution of indoor radon measurements: a preliminary data base. JAPCA 37(3):227–231.

Briggs D, Abellan JJ, Fecht D. 2008. Environmental inequity in England: small area associations between socio-economic status and environmental pollution. Soc Sci Med 67(10):1612–1629.

Cohen BL, Gromicko N. 1988. Variation of radon levels in U.S. homes with various forms. JAPCA 38(2):129–134.

Cox C. 1998. Delta method. In: Encyclopedia of Biostatistics (Armitage P, Colton T, eds). New York:John Wiley, 1125–1127.

Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. 2005. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 330(7485):223; doi:10.1136/bmj.38308.477650.63.

Folger PF, Nyberg P, Wanty RB, Poeter E. 1994. Relationships between 222Rn dissolved in ground water supplies and indoor 222Rn concentrations in some Colorado front range houses. Health Phys 67(3):245–253.

Gogolak CV. 1980. Review of ^{222}Rn in Natural Gas Produced from Unconventional Sources. New York:U.S. Department of Energy. Available: http://treichlerlawoffice.com/radiation/DOEuranium653239.pdf [accessed 8 March 2015].

Gross EL. 2013. Distribution of Indoor Radon Concentrations in Pennsylvania, 1990–2007. U.S. Geological Survey Scientific Investigations Report 2013–5143. Available: http://pubs.usgs.gov/sir/2013/5143/pdf/sir2013-5143.pdf [accessed 1 June 2014].

Gundersen LCS. 1991. Radon in sheared metamorphic and igneous rocks. In: Field Studies of Radon in Rocks, Soils and Water (Gundersen LCS, Wanty RB, eds). Boca Raton, FL:CRC Press, 39–49.

Hardin JW, Hilbe JM. 2013. Generalized Estimating Equations. 2nd ed. Boca Raton, FL:CRC Press.

Johnson N. 2010. Pennsylvania Energy Impacts Assessment, Report 1: Marcellus Shale Natural Gas and Wind. Available: http://www.nature.org/media/pa/pa_energy_assessment_report.pdf [accessed 2 July 2014].

Johnson RH Jr, Bernhardt DE, Nelson NS, Calley HW Jr. 1973. Assessment of Potential Radiological Health Effects from Radon in Natural Gas. EPA-520/1-73-004. Washington, DC:U.S. EPA, Office of Radiation Programs. Available: http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91012JNH.TXT [accessed 8 March 2015].

NRC (National Research Council). 1999a. Health Effects of Exposure to Radon: BEIR VI. Washington, DC:National Academy Press.

NRC (National Research Council). 1999b. Risk Assessment of Radon in Drinking Water. Washington, DC:National Academies Press.

Pawel DJ, Puskin JS. 2004. The U.S. Environmental Protection Agency's assessment of risks from indoor radon. Health Phys 87(1):68–74.

Perma-Fix Environmental Services Inc. 2015. Technologically Enhanced Naturally Occurring Radioactive Materials (TENORM) Study Report. Harrisburg, PA:Pennsylvania Department of Environmental Protection. Available: http://www.elibrary.dep.state.pa.us/dsweb/Get/Document-105822/PA-DEP-TENORM-Study_Report_Rev._0_01-15-2015.pdf [accessed 12 March 2015].

R Core Team. 2013. R: A Language and Environment for Statistical Computing. Vienna, Austria:R Foundation for Statistical Computing. Available: http://www.R-project.org [accessed April 2013].

Rich AL, Crosby EC. 2013. Analysis of reserve pit sludge from unconventional natural gas hydraulic fracturing and drilling operations for the presence of technologically enhanced naturally occurring radioactive material (TENORM). New Solut 23(1):117–135.

Rowan EL, Engle MA, Kirby CS, Kraemer TF. 2011. Radium Content of Oil- and Gas-Field Produced Waters in the Northern Appalachian Basin (USA): Summary and Discussion of Data. U.S. Geological Survey Scientific Investigations Report 2011–5135. Available: http://pubs.usgs.gov/sir/2011/5135/ [accessed 25 June 2014].

Rowan EL, Kraemer T. 2012. Radon-222 Content of Natural Gas Samples from Upper and Middle Devonian Sandstone and Shale Reservoirs in Pennsylvania: Preliminary Data. U.S. Geological Survey Open-File Report 2012–1159. Available: http://pubs.usgs.gov/of/2012/1159 [accessed 30 June 2014].

Schwartz BS, Stewart WF, Godby S, Pollak J, DeWalle J, Larson S, et al. 2011. Body mass index and the built and social environments in children and adolescents using electronic health records. Am J Prev Med 41(4):e17–e28.

Swistock BR, Sharpe WE, Robillard PD. 1993. A survey of lead, nitrate and radon contamination of private individual water systems in Pennsylvania. J Environ Health 55(5):6–12.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). 2009. UNSCEAR 2006 Report, Annex E. Sources-to-Effects Assessment for Radon in Homes and Workplaces. United Nations, New York. Available: http://www.unscear.org/docs/reports/2006/09-81160_Report_Annex_E_2006_Web.pdf [accessed 8 March 2015].

U.S. EPA (U.S. Environmental Protection Agency). 1992. Technical Support Document for the 1992 Citizen's Guide to Radon. EPA-400-R-92-11. Washington, DC:U.S. EPA. Available: http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=000001L3.TXT [accessed 8 March 2015].

U.S. EPA (U.S. Environmental Protection Agency). 2008. Technical Report on Technologically Enhanced Naturally Occurring Radioactive Materials from Uranium Mining. Vol. 1. Mining and Reclamation Background. EPA 402-R-08-005. Washington, DC:U.S. EPA. Available: http://www.epa.gov/radiation/docs/tenorm/402-r-08-005-voli/402-r-08-005-v1.pdf [accessed 8 March 2015].

Warner NR, Jackson RB, Darrah TH, Osborn SG, Down A, Zhao K, et al. 2012. Geochemical evidence for possible natural migration of Marcellus Formation brine to shallow aquifers in Pennsylvania. Proc Natl Acad Sci USA 109(30):11961–11966.

World Health Organization. 2009. WHO Handbook on Indoor Radon: A Public Health Perspective. Geneva:WHO Press. Available: http://www.nrsb.org/pdf/WHO Radon Handbook.pdf [accessed 8 March 2015].

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

Associations between Unconventional Natural Gas Development and Nasal and Sinus, Migraine Headache, and Fatigue Symptoms in Pennsylvania

Aaron W. Tustin, Annemarie G. Hirsch, Sara G. Rasmussen, Joan A. Casey, Karen Bandeen-Roche, and Brian S. Schwartz

http://dx.doi.org/10.1289/EHP281

Received: 22 December 2015
Revised: 29 July 2016
Accepted: 31 July 2016
Published: 25 August 2016

Environ Health Perspect DOI: 10.1289/EHP281
Advance Publication: Not Copyedited

Associations between Unconventional Natural Gas Development and Nasal and Sinus, Migraine Headache, and Fatigue Symptoms in Pennsylvania

Aaron W. Tustin[1], Annemarie G. Hirsch[2], Sara G. Rasmussen[1], Joan A. Casey[3], Karen Bandeen-Roche[4], and Brian S. Schwartz[1,2,5]

[1]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Center for Health Research, Geisinger Health System, Danville, Pennsylvania, USA; [3]Robert Wood Johnson Health and Society Scholars Program, University of California at San Francisco and Berkeley, USA; [4]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [5]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Corresponding author: Brian S. Schwartz, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Room W7041, Baltimore, MD 21205. Telephone: (410) 955-4158. Fax: (410) 955-1811. E-mail: bschwar1@jhu.edu.

Running title: Fracking and sinusitis, migraine, and fatigue

Acknowledgments: This research was funded by National Institutes of Health U19 AI106683 (PI Robert Schleimer), R21 ES023675 (PI Brian Schwartz), and training grant ES07141 (Sara Rasmussen); the Robert Wood Johnson Foundation (Joan Casey); the Degenstein Foundation; and the National Science Foundation Integrative Graduate Education and Research Traineeship (Sara Rasmussen).

Competing Financial Interests: Dr. Schwartz is a Fellow of the Post Carbon Institute (PCI), serving as an informal advisor on climate, energy, and health issues. He receives no payment for this role. His research is entirely independent of PCI, and is not motivated, reviewed, or funded by PCI. The other authors declare they have no actual or potential competing financial interests.

ABSTRACT

Background: Unconventional natural gas development (UNGD) produces environmental contaminants and psychosocial stressors. Despite these concerns, few studies have evaluated the health effects of UNGD.

Objectives: We investigated associations between UNGD activity and symptoms in a cross-sectional study in Pennsylvania.

Methods: We mailed a self-administered questionnaire to 23,700 adult patients of the Geisinger Clinic. Using standardized and validated questionnaire items, we identified respondents with chronic rhinosinusitis (CRS), migraine headache, and fatigue symptoms. We created a summary UNGD activity metric that incorporated well phase, location, total depth, daily gas production and inverse distance-squared to patient residences. We used logistic regression, weighted for sampling and response rates, to assess associations between quartiles of UNGD activity and outcomes, both alone and in combination.

Results: The response rate was 33%. Of 7,785 study participants, 1,850 (24%) had current CRS symptoms, 1,765 (23%) had migraine headache, and 1,930 (25%) had higher levels of fatigue. Among individuals who met criteria for two or more outcomes, adjusted odds ratios for the highest quartile of UNGD activity compared to the lowest were [OR (95% CI)] 1.49 (0.78, 2.85) for CRS plus migraine, 1.88 (1.08, 3.25) for CRS plus fatigue, 1.95 (1.18, 3.21) for migraine plus fatigue, and 1.84 (1.08, 3.14) for all three outcomes together. Significant associations were also present in some models of single outcomes.

Conclusions: This study provides evidence that UNGD is associated with nasal and sinus, migraine headache, and fatigue symptoms in a general population representative sample.

INTRODUCTION

Unconventional natural gas development (UNGD), which includes the process of hydraulic fracturing, represents an expanding share of energy production worldwide. Shale gas extraction now comprises 40% of U.S. domestic natural gas production (Energy Information Administration 2015). In the past decade particularly rapid increases in UNGD have occurred in Pennsylvania, where more than 8,800 unconventional wells have been drilled.

There are concerns that UNGD could affect the environment via chemical pollutants such as diesel exhaust, volatile organic compounds, combustion products, fugitive emissions, and fracking chemicals (Werner et al. 2015). UNGD has been linked to contamination of air (Macey et al. 2014; Paulik et al. 2015), soil (Maloney and Yoxtheimer 2012), groundwater (Jackson et al. 2013; Drollette et al. 2015), and surface water (Kassotis et al. 2014). UNGD also creates contextual and psychosocial stressors including noise, truck traffic, influxes of non-local workers, and perceived negative impacts on quality of life and the built and social environments (Saberi et al. 2014; Powers et al. 2015; Adgate et al. 2014).

There have been few studies of the health effects of UNGD, despite increasing concern (Mitka 2012; Kovats et al. 2014). Prior studies have been limited by factors including small sample size and imprecise exposure assessment (Adgate et al. 2014). Because expansion of UNGD has outpaced scientific understanding of its potential health impacts, studies of self-reported outcomes have been advocated as a rapid means of generating hypotheses that could influence public policy. Furthermore, some illnesses with plausible links to UNGD, such as pain syndromes and fatigue, are defined solely by symptoms. Yet to date there have been only two epidemiologic studies, each with fewer than 500 participants, of symptoms in relation to UNGD (Steinzor et al. 2013; Rabinowitz et al. 2015).

We used data from a large population-based cross-sectional survey of Pennsylvania adults to identify patients with nasal and sinus symptoms, migraine headache, and higher levels of fatigue. We selected these outcomes because of their high prevalence, large economic costs, and possible links to environmental risk factors through chemical toxicity, irritation, odors, or stress (Hastan et al. 2011; Bhattacharyya 2009; Shashy et al. 2004; Tan et al. 2013; Friedman and De ver Dye 2009; Sjostrand et al. 2010; Bell et al. 1998; Griffith and Zarrouf 2008; Ranjith 2005; Ricci et al. 2007). The purpose of this study was to test the null hypothesis that UNGD is not associated with these three outcomes. To do so, we conducted a case-control analysis in which we compared individuals with one or more of these health outcomes to selected participants with no or minimal evidence of these diseases.

METHODS

Study overview

In early 2014, we performed a cross-sectional survey of primary care patients of the Geisinger Clinic. Information was gathered via a questionnaire designed to study general CRS epidemiology (for questionnaire see Supplemental Material, "Population Study of Nasal and Sinus Symptoms"). The questionnaire did not mention UNGD because that was not its primary purpose. We used residential addresses and information about Pennsylvania unconventional gas wells to create UNGD activity metrics for four time-varying well development phases. We evaluated the associations between UNGD activity and CRS, migraine headache, and fatigue symptoms. The study protocol was approved by the Institutional Review Board (IRB) of the Geisinger Health System with an IRB Authorization Agreement with the Johns Hopkins Bloomberg School of Public Health. Waivers of HIPAA authorization and written informed

consent were approved by the IRB; implied consent was considered to have been provided if the patient returned the mailed questionnaire.

Study population

The Geisinger Clinic provides primary care services to over 400,000 patients, predominantly in central and northeastern Pennsylvania. Our source population consisted of 200,769 adult (age ≥ 18 years) Geisinger primary care patients for whom we had electronic health record (EHR) data and information on race/ethnicity. From this source population we selected 23,700 survey recipients using a stratified sampling design which is described in the following section. We mailed the baseline questionnaire in April 2014. A total of 7,847 (33.1%) individuals returned the questionnaire after three mailings. Questionnaires were returned between April 13 and October 13, 2014. After excluding respondents who lived outside Pennsylvania (n = 62), the study sample consisted of 7,785 participants.

Rationale and description of the stratified sampling method

We oversampled racial/ethnic minorities because a primary interest of the parent grant was to understand racial/ethnic differences in CRS epidemiology. Geisinger's catchment area only has approximately 8% racial/ethnic minorities. Oversampling was necessary to ensure a sufficient number of racial/ethnic minorities in the parent study.

Similarly, to ensure an adequate number of CRS patients in the parent CRS study, we oversampled individuals with higher likelihood of having CRS. To do so, we used electronic health record data to identify Geisinger primary care patients with higher, intermediate, and lower likelihood of CRS. These assessments were based on International Classification of

Disease (ICD)-9 codes and Current Procedural Terminology (CPT) codes from the medical record. Patients with a "higher" likelihood of CRS (n = 13,494) had at least two ICD-9 codes for CRS (ICD-9 codes 473.x or 471.x) associated with an outpatient, inpatient, or emergency department encounter; or at least one CPT code for sinus computerized tomography, sinus endoscopy, or sinus surgery. Patients with "intermediate" likelihood of CRS (n = 49,918) had at least one ICD-9 code for asthma (493.x) or allergic rhinitis (477.x); or a single ICD-9 code for CRS associated with an outpatient, inpatient, or emergency department encounter. The 137,357 patients who did not meet criteria for the higher and intermediate likelihood groups were designated as having a "lower" likelihood of CRS.

We divided our source population into six strata based on race/ethnicity and likelihood of CRS. We mailed the baseline CRS survey to a larger percentage of individuals in the strata of interest (see Supplemental Material, Table S1).

Covariates

From the EHR we obtained these covariates: sex; current age (years); race/ethnicity (white non-Hispanic, other); smoking status (never, current, former); body mass index (BMI, kg/m^2); residential address; and history of receiving Medical Assistance, a means-tested health insurance program that we used as a surrogate for family socioeconomic status (Casey et al. 2013). We used information in the EHR to derive each individual's residential place type (township, borough, or census tract in cities) and Charlson comorbidity index. We computed the Charlson index, which incorporates the number and severity of comorbid illnesses, consistent with previously published criteria (Charlson et al. 1987). We dichotomized race/ethnicity because only 10% of participants were non-white, which is reflective of the general population in

these communities (Casey et al. 2016). Our questionnaire ascertained additional information on educational status, marital status, household income, hay fever, nasal polyps, age at onset of nasal/sinus symptoms (in 5-year categories), history of sinus surgery, and current use of sinusitis medications (antibiotics and oral, inhaled, and nasal corticosteroids). We used United States census data to derive community socioeconomic deprivation (CSD) in townships, boroughs, and cities using a modified version of the Townsend index (Townsend 1987) as previously reported (Liu et al. 2012).

Outcome ascertainment

The cardinal symptoms of CRS are nasal congestion/obstruction, nasal discharge (anterior or posterior nasal drip), smell loss, and facial pain or pressure. Our questionnaire ascertained the frequency ("never," "once in a while," "some of the time," "most of the time," or "all the time"), in the past three months, of the aforementioned symptoms (questions 10-15 of the questionnaire, which is included in the Supplemental Material, "Population Study of Nasal and Sinus Symptoms"). Following European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) diagnostic criteria for CRS in epidemiologic studies (Fokkens et al. 2012), we determined participants to have current CRS if they experienced two or more cardinal symptoms (one of which must be nasal congestion/obstruction [question 10] or discharge [question 11 and/or 12]) at least "most of the time" in the past three months.

We ascertained migraine headache via questions from the ID Migraine questionnaire (Lipton et al. 2003) covering the past twelve months. Those with headaches at least "some of the time" (question 80) were asked the frequency ("never," "rarely," "less than half the time," "half the time or more") of headache-associated disability, nausea, and photophobia (questions 81-83).

Using a validated scoring method (Lipton et al. 2003), we dichotomized the three responses. Responses of "never" or "rarely" were scored as no and responses of "less than half the time" or "half the time or more" were scored as yes. Participants who answered yes to at least two of three questions were considered to have migraines.

We ascertained fatigue with eight questions from the PROMIS fatigue short form 8a (Patient-Reported Outcomes Measurement Information System 2015). These items assessed the frequency ("not at all," "a little bit," "somewhat," "quite a bit," "very much") of fatigue and fatigue-related disability in the past week (questions 84-91). We used the instrument's standardized scoring instructions to code responses from 1 ("not at all") to 5 ("very much") and summed the eight values to produce a score ranging from 8 to 40. We excluded individuals who answered fewer than four questions (n = 76). Individuals who answered between 4 and 7 questions were assigned a pro-rated score using this formula: score = (raw sum x 8)/(number of items answered). Fractional scores were rounded up to the nearest integer. Our "higher levels of fatigue" outcome consisted of individuals in the highest quartile (score $\geq$ 28).

Some respondents met criteria for more than one outcome. In the analysis, we evaluated associations of UNGD with single outcomes (i.e., CRS only; migraine only; or fatigue only) and multiple outcomes (i.e., participants with CRS and migraine; CRS and fatigue; migraine and fatigue; or all three outcomes).

Reference group

We performed an unmatched case-control analysis in which we compared individuals with one or more of the three primary outcomes ("cases") to a subset of participants with no or minimal evidence of these outcomes (hereafter referred to as "controls" or the "reference

group"). The reference group comprised study participants who 1) did not meet diagnostic criteria for past or current CRS, 2) reported no migraine headache symptoms, and 3) reported lower levels of fatigue (i.e., first quartile of fatigue score). Individuals with past CRS, intermediate likelihood of migraine, and/or moderate levels of fatigue were excluded from the reference group. These exclusion criteria were intended to produce a reference group free of individuals with a moderate likelihood of having the outcome (in the case of migraine and fatigue) or whose disease had been aggressively managed and treated (in the case of past CRS).

We created the reference group as follows. First, we excluded all study participants with one or more of the outcomes of interest. Next, individuals who met criteria for lifetime CRS (i.e., responses of "yes" to at least two cardinal symptoms on questions 1-6, one of which had to be nasal blockage [question 1] or discharge [question 2 and/or 3]) but not current CRS were deemed to have "past CRS" and were excluded from the reference group. We then excluded participants from the reference group if they endorsed any of the three ID Migraine criteria. In other words, members of the reference group either skipped the ID Migraine questions (e.g., because they reported a headache frequency of "never" or "once in a while" on question 80 and were instructed to skip the following three questions) or responded to questions 81-83 with no migraine symptom occurring more frequently than "never" or "rarely." Finally, we excluded individuals from the reference group if their fatigue score was higher than the 25th percentile (i.e., those with fatigue score > 13) or they did not answer at least four of eight PROMIS fatigue items (questions 84-91). No other inclusion or exclusion criteria were applied to the reference group.

UNGD activity assessment

We used published descriptions, and our own data, to estimate the duration of each UNGD phase (Gaines 2013; New York State Department of Environmental Conservation 2015; Casey et al. 2016). Pad preparation, which involves the clearing of the well site, lasts approximately 30 days. Drilling of the well then takes 1 to 30 days, proportionate to the total (vertical plus horizontal) depth. After drilling, hydraulic fracturing occurs during a stimulation (fracking) phase that lasts an average of 7 days. Finally, the well produces natural gas during a production phase that lasts months to years.

To capture these complexities of well development, we compiled data on UNGD in Pennsylvania from January 1, 2005 through December 31, 2014, from the Pennsylvania Department of Environmental Protection, the Pennsylvania Department of Conservation and Natural Resources, and SkyTruth (http://skytruth.org). For each well we obtained geographic coordinates; start dates of drilling, stimulation, and production; total depth; and volume of natural gas produced during six- or twelve-month reporting windows.

Using methods described previously (Casey et al. 2016), we created UNGD activity metrics for each phase of well development. Briefly, metrics incorporated all unconventional gas wells in Pennsylvania and were defined as

$$\text{Metric for participant } i = \frac{1}{T}\sum_{t=-1}^{-T}\sum_{j=1}^{n} w_j(t)/\, d_{ij}^2$$

where T was an averaging period in days (in our primary analysis, $T = 90$ because CRS diagnostic criteria require three months of symptoms); t was a temporal summation index whose negative sign represents past dates (e.g., summing from $t = -1$ to -90 indicates that the metric was averaged over 90 consecutive days immediately prior to the survey); n was the number of wells;

$w_j(t)$ was the weight assigned to the *j*th well on day *t*; and d_{ij}^2 was the squared distance between well *j* and the residential address of participant *i*. We set $w_j(t) = 0$ for wells that were inactive in the given phase on day *t*. Active wells were assigned weights during the duration of the relevant phase as follows: for pad preparation and drilling metrics, $w_j(t)$ was 1; for the stimulation metric, $w_j(t)$ was the total depth (a surrogate for hydraulic fracturing chemical volumes and the number of truck trips required to transport stimulation materials); and for the production metric, $w_j(t)$ was the average daily volume of natural gas produced during the corresponding reporting period.

Because the four UNGD phase metrics were highly correlated when averaged over 90 days (Spearman coefficient > 0.90 for each pairwise comparison), we *z*-transformed the metrics and summed the resulting *z*-scores. For analysis, we divided this continuous composite UNGD activity metric into quartiles for ease of interpretation and because of its skewed distribution.

Statistical analysis

We used descriptive statistics to compare characteristics of participants with and without each outcome. To evaluate selection bias with respect to UNGD, we compared distributions of the UNGD activity metric in study participants and questionnaire non-responders. To assess the potential for non-conservative errors due to selection bias with respect to health status, we analyzed distributions of the Charlson comorbidity index in study participants and survey non-responders, stratified by UNGD quartile. Categorical and continuous variables were compared using χ^2 tests and *t*-tests, respectively. For hypothesis testing, *p*-values < 0.05 were considered statistically significant.

We used weighted logistic regression to evaluate associations between UNGD activity and symptoms while adjusting for confounding variables. All models compared individuals with

the outcome(s) of interest ("cases") to the reference group described above ("controls"). The use of sampling weights allowed us to account for the differential patient selection and participation rates in our stratified design, while targeting unbiased measures of association and obtaining robust standard errors. We assigned each participant a sampling weight equal to the inverse probability of inclusion in the study (see Supplemental Material, Table S1). Because the weight in one stratum (150.8) was very substantially larger than the other weights, we truncated this weight by reducing it to the value of the second-highest weight (32.3).

We adjusted all models for these potential confounders that we identified *a priori*: sex, race/ethnicity (non-Hispanic white vs. other), age (linear and quadratic terms; to avoid collinearity we centered the age variable by subtracting its mean [i.e., $A_c = A_i - A_{mean}$]), receipt of Medical Assistance (never vs. ever), and smoking status (never vs. former and current). We tested for additional confounding by adding linear and quadratic terms for BMI and CSD. We retained these covariates in the models if they changed associations between UNGD and the outcome by at least 10%. Analyses were performed in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 13.1 (StataCorp, College Station, Texas) using the svy commands.

We reasoned that UNGD might be associated with current CRS only for onset of symptoms after 2006, when UNGD commenced in Pennsylvania. To test the associated hypothesis we stratified the CRS group by date of symptom onset (before/after January 1, 2006) and re-ran models within each stratum. While associations of UNGD activity with our other outcomes could also differ by onset date, our questionnaire did not ascertain the onset date of migraine and fatigue symptoms.

We performed several sensitivity analyses. To explore the impact of sampling weight

choices, we re-ran models with full (i.e., not truncated) weights and again with no weights. To determine whether associations differed by the length of the UNGD assessment period, we compared associations using 7-day, 90-day, and 365-day averaged UNGD metrics that corresponded to the questionnaire's recall windows for the three primary outcomes. To explore spatial differences among groups of participants, we mapped the residential locations of individuals with and without our primary outcomes, stratified by UNGD quartile and case/control status. To assess whether UNGD was associated with symptoms in individuals with past disease or moderate symptoms, we created additional CRS and fatigue models in which we re-classified some previously excluded individuals as "cases" (for details see Supplemental Material, "Models of Past Disease and Moderate Symptoms"). To assess whether unmeasured confounding, including spatial confounding, could be responsible for the observed associations, we created "negative control outcome" models (Lipsitch et al. 2010). These adjusted logistic regression models evaluated associations between UNGD and self-reported outcomes (bad breath, ear pain, and cold/flu symptoms) that we thought were unlikely to be related to UNGD. We expected to find no significant associations between UNGD and these outcomes; the presence of such associations could indicate bias due to unmeasured confounding. In these models, we defined cases as all study participants who reported the symptom at least "most of the time" in the past three months (questions 36, 43, and 48 for bad breath, ear pain, and cold/flu symptoms, respectively). The reference group for each model consisted of all individuals who reported the symptom "never" in the past three months.

RESULTS

Characteristics of the study population

Questionnaire respondents were 7,785 individuals from 39 counties in central and northeastern Pennsylvania, in regions with and without UNGD (Figure 1). Compared to questionnaire recipients who did not respond, our study population was more likely to be female, white, and older (results not shown). The continuous UNGD activity metric did not differ significantly ($p = 0.26$) between study participants and questionnaire non-responders (Table 1). Study participants were less likely than non-responders to be in the highest UNGD quartile. While the Charlson comorbidity index was higher in responders (mean = 3.43) than in non-responders (mean = 2.52, $p < 0.001$), the mean Charlson values were similar across all UNGD quartiles (Table 1).

We identified 738 participants with current CRS and no other primary outcome, 580 with migraine headache only, and 666 with higher levels of fatigue only (Table 2). These conditions were co-occurring in other individuals. There were 268 individuals with CRS and migraine, 347 with CRS and higher levels of fatigue, 420 with migraine and higher levels of fatigue, and 497 with all three outcomes. There were 1,380 participants with no current or past CRS, no migraine headache symptoms, and lower levels of fatigue; these comprised the reference group. Compared to the reference group, individuals with each single outcome were more likely to be younger and current smokers (Table 2). Those with migraine and fatigue were more likely to be female, while those reporting CRS and fatigue were more likely to be white non-Hispanic.

Associations of UNGD with symptoms

The highest quartile of UNGD activity, compared to the lowest, was associated with

significantly increased odds of the following combinations of two or more outcomes: CRS and higher levels of fatigue [odds ratio (OR) = 1.88; 95% confidence interval (CI): 1.08, 3.25]; migraine headache and higher levels of fatigue (OR = 1.95; 95% CI: 1.18, 3.21); and all three outcomes (OR = 1.84; 95% CI: 1.08, 3.14) (Table 3). The second and third quartiles of UNGD were not significantly associated with any of the outcomes. In individuals with only one outcome, the odds ratios for the fourth quartile of UNGD were 1.11 (95% CI: 0.75, 1.65) for current CRS, 1.43 (95% CI: 0.94, 2.18) for migraine headache, and 1.47 (95% CI: 0.996, 2.18) for higher levels of fatigue (Table 3). In general, participants in the fourth quartile of UNGD lived farther north than those in other UNGD quartiles (Figure 2).

When we stratified CRS patients by onset date, the second (OR = 3.27; 95% CI: 1.21, 8.82) and fourth (OR = 3.26; 95% CI: 1.14, 9.36) quartiles of UNGD were associated with significantly increased odds of CRS in those whose symptoms began after 2006 (see Supplemental Material, Table S2). There were no associations in participants with earlier symptom onset.

Sensitivity analyses

In participants with multiple outcomes, most inferences were unchanged whether we used the full sampling weights, truncated weights, or no weights (compare Table 3 to Supplemental Material, Table S3). Odds ratios for the fourth quartile of UNGD were consistently higher, and had wider confidence intervals, in fully weighted models than in models with truncated weights. For example, the odds ratio for the association of the fourth quartile of UNGD with the co-existence of migraine and fatigue was 2.89 (95% CI: 1.45, 5.76) in the fully weighted model. In individuals with single outcomes, the fourth quartile of UNGD was significantly associated with

migraine headache (OR = 1.80; 95% CI: 1.02, 3.17) and fatigue (OR = 1.89; 95% CI: 1.10, 3.26) in the models with full weights; significant associations were also present in unweighted models (see Supplemental Material, Table S3).

UNGD activity, when averaged over 7 or 365 days, was highly correlated with the 90-day time-averaged UNGD metric used in the primary analyses (Spearman coefficient = 0.98 for both comparisons). Most inferences and associations were similar when using a 7-day or 365-day averaging period (see Supplemental Material, Table S4). The second quartile of UNGD was associated with past CRS but there were no associations of UNGD with moderate levels of fatigue (see Supplemental Material, Table S5). UNGD was not associated with the negative control outcomes of ear pain, bad breath, or cold/flu symptoms (Table 4).

Because only the highest level of UNGD was associated with our primary outcomes, we compared demographic and socioeconomic characteristics of individuals in the fourth quartile of UNGD to those of participants in other UNGD quartiles (see Supplemental Material, Table S6). Participants in the fourth quartile of UNGD differed on some covariates, several of which were included in the final models. We did not include place type in the final adjusted models because it could be a surrogate for mediators (e.g., individual- or place-level socioeconomic status) of associations between UNGD and symptoms. In a sensitivity analysis that explored the effect of place type, some associations were attenuated slightly when place type was added to the models, but inferences were similar (see Supplemental Material, Table S7).

DISCUSSION

In our survey of primary care patients in central and northeast Pennsylvania, residential UNGD activity was associated with nasal and sinus symptoms, migraine headache, and higher

levels of fatigue, either alone or in combination. Our findings are suggestive of a threshold in the relationship between UNGD and symptoms, as associations were present only among participants in the fourth quartile of UNGD activity. We found stronger associations in individuals with two or more co-occurring outcomes. In addition, UNGD was associated with CRS in individuals whose nasal and sinus symptoms began after the start of UNGD in Pennsylvania, although these estimates had lower precision due to the small number of subjects with recent CRS onset.

In surveys such as ours, in which selection is based on the outcome, regression models must include sampling weights (or employ another strategy to acknowledge the selection mechanism) to avoid bias. However, extreme sampling weights can significantly increase the model's variance (Potter 1988). To balance bias reduction against variance inflation, several techniques have been developed to truncate large sampling weights. We employed one such technique in our primary analyses. We found associations between UNGD and symptoms in the primary models, and in fully weighted and unweighted models.

There is limited prior evidence linking environmental factors to CRS, migraine headache, and fatigue. Exposure to allergens, toxicants, and secondhand smoke may trigger nasal and sinus symptoms (Fokkens et al. 2012). However, a recent review found insufficient epidemiologic evidence from which to draw conclusions about occupational or environmental risk factors for CRS (Sundaresan et al. 2015). Though migraines have a strong hormonal and genetic component, migraines can also be triggered by noise, odors, and stress (Friedman and De ver Dye 2009; Sjostrand et al. 2010; Sauro and Becker 2009). Similarly, fatigue has multiple risk factors including sleep deprivation, psychosocial stressors, medical disorders, psychiatric factors, occupation, and exposure to low levels of environmental chemicals (Bell et al. 1998; Ranjith

2005; Ricci et al. 2007; Griffith and Zarrouf 2008). Our UNGD activity metrics were designed to capture all potential environmental pathways that could affect these symptoms.

We did not measure participants' exposure to ambient air pollution. We also did not account for conventional oil and gas wells. During our study period the production of conventional gas wells in Pennsylvania was very low compared to that of unconventional wells. Furthermore, Pennsylvania's conventional wells tend to be in the northwest and west, where Geisinger has no patients. The lack of significant geographic overlap with our study population makes confounding of UNGD associations by conventional oil and gas wells unlikely.

Participants in the fourth quartile of UNGD activity lived farther north than those in other quartiles (Figure 2). This spatial separation is due to the location of the Marcellus shale, which constrains UNGD to the northern portion of the Geisinger catchment area. Given the correlation between geography and UNGD, we cannot rule out the possibility that spatial confounding was responsible for the observed associations. However, we note that our models were adjusted for several covariates (such as race/ethnicity and socioeconomic status) that could be associated with both location and outcomes. In addition, the null results in our negative control outcome models did not suggest spatial confounding.

CRS, migraine headache, and fatigue are highly prevalent and produce significant societal costs. CRS affects 2-16% of U.S. adults and results in emergency department visits, antibiotic prescriptions, sinus surgeries, and direct healthcare costs (Hastan et al. 2011; Bhattacharyya 2009; Shashy et al. 2004; Tan et al. 2013). Migraines have a prevalence of 11-14% and cause substantial temporary disability, emergency department visits, outpatient clinic visits, and analgesic use (Lipton et al. 2007; Burch et al. 2015). Fatigue prevalence, defined in various ways across studies, is estimated at 7-45%, and fatigue costs U.S. employers over $100

billion per year in lost productive work time (Ricci et al. 2007). From a public health and economic perspective it is vital to understand modifiable risk factors for these illnesses.

Recent reviews have noted the lack of high-quality evidence regarding the health effects of UNGD (Adgate et al. 2014; Werner et al. 2015). Our study of 7,785 Pennsylvania residents is the largest survey of symptoms with respect to UNGD and has several strengths when compared to prior studies. We selected a population-based adult sample with no exclusion criteria. Reporting bias was minimized by the fact that UNGD was not identified as a study aim, and response rates did not differ by proximity to UNGD. Our time-varying UNGD activity metric incorporated well phase and intensity measures such as total depth and gas production. We used standardized and validated instruments to assess fatigue and migraine, respectively, and we used consensus epidemiologic guidelines to assess CRS.

This study had several limitations. In general, cross-sectional surveys such as ours cannot assess temporal relations between exposures and outcomes, and we did not ascertain the onset dates of some symptoms. We note, however, that our UNGD activity metrics could theoretically be used to establish temporality, as they can be computed for any date prior to symptom onset. Our ascertainment of self-reported outcomes was susceptible to various types of information bias. For example, despite the fact that our questionnaire did not mention UNGD, individuals residing near UNGD may have over-reported symptoms. There was some evidence of selection bias, as survey participants had poorer health (measured by the Charlson comorbidity index) than non-responders. However, differences in health status were similar across levels of UNGD activity. Another limitation is that our estimates of well development phase durations, although based on published average values, may have been incorrect for individual wells. Further exposure misclassification could have occurred because our UNGD activity metric was based on

residential addresses. Participants' exposure to UNGD activity could have been affected by unmeasured factors such as occupation, travel, and time spent outdoors. Additionally, our UNGD activity metric did not allow identification of specific exposures or exposure pathways.

CONCLUSIONS

UNGD was associated with CRS, migraine headache, and fatigue symptoms in a large population-based survey. Associations were stronger in patients with two or more outcomes. Our work has several advantages over previous studies, making it an important addition to the growing body of evidence that UNGD is associated with adverse health effects. Further research, including more sophisticated exposure and outcome measurements, is necessary to evaluate whether these associations are causal and to elucidate the mechanisms for these findings.

REFERENCES

Adgate JL, Goldstein BD, McKenzie LM. 2014. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol 48(15):8307-8320.

Bell IR, Baldwin CM, Schwartz GE. 1998. Illness from low levels of environmental chemicals: Relevance to chronic fatigue syndrome and fibromyalgia. Am J Med 105(3A):74S-82S.

Bhattacharyya N. 2009. Contemporary assessment of the disease burden of sinusitis. Am J Rhinol Allergy 23(4):392-395.

Burch RC, Loder S, Loder E, Smitherman TA. 2015. The prevalence and burden of migraine and severe headache in the United States: Updated statistics from government health surveillance studies. Headache 55(1):21-34.

Casey JA, Curriero FC, Cosgrove SE, Nachman KE, Schwartz BS. 2013. High-density livestock operations, crop field application of manure, and risk of community-associated methicillin-resistant Staphylococcus aureus infection in Pennsylvania. JAMA Intern Med 173(21):1980-1990.

Casey JA, Savitz DA, Rasmussen SG, Ogburn EL, Pollak J, Mercer DG, et al. 2016. Unconventional natural gas development and birth outcomes, Pennsylvania, USA. Epidemiology 27(2):163-72.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 40(5):373-383.

Drollette BD, Hoelzer K, Warner NR, Darrah TH, Karatum O, O'Connor MP, et al. 2015. Elevated levels of diesel range organic compounds in groundwater near Marcellus gas

operations are derived from surface activities. Proc Natl Acad Sci USA 112(43):13184-13189.

Energy Information Administration. 2015. U.S. natural gas gross withdrawals and production. Available: http://www.eia.gov/dnav/ng/ng_prod_sum_dcu_NUS_a.htm [accessed 3 November 2015].

Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. 2012. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl 23:3 p preceding table of contents, 1-298.

Friedman DI, De ver Dye T. 2009. Migraine and the environment. Headache 49(6):941-952.

Gaines M. 2013. Shale Energy Development's Effect on the Posting, Bonding, and Maintenance of Roads in Rural PA. Available: http://extension.psu.edu/natural-resources/natural-gas/webinars/shale-energy-developments-effect-on-the-posting-bonding-and-maintenance-of-roads-in-rural-pa [accessed 30 October 2015].

Griffith JP, Zarrouf FA. 2008. A systematic review of chronic fatigue syndrome: Don't assume it's depression. Prim Care Companion J Clin Psychiatry 10(2):120-128.

Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. 2011. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy 66(9):1216-1223.

Jackson RB, Vengosh A, Darrah TH, Warner NR, Down A, Poreda RJ, et al. 2013. Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. Proc Natl Acad Sci USA 110(28):11250-11255.

Kassotis CD, Tillitt DE, Davis JW, Hormann AM, Nagel SC. 2014. Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. Endocrinology 155(3):897-907.

Kovats S, Depledge M, Haines A, Fleming LE, Wilkinson P, Shonkoff SB, et al. 2014. The health implications of fracking. Lancet 383(9919):757-758.

Lipsitch M, Tchetgen ET, Cohen T. 2010. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 21(3):383-388.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF, et al. 2007. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 68(5):343-349.

Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J, Hettiarachchi J, et al. 2003. A self-administered screener for migraine in primary care: The ID migraine validation study. Neurology 61(3):375-382.

Liu AY, Curriero FC, Glass TA, Stewart WF, Schwartz BS. 2012. Associations of the burden of coal abandoned mine lands with three dimensions of community context in Pennsylvania. ISRN Public Health 2012:251201.

Macey GP, Breech R, Chernaik M, Cox C, Larson D, Thomas D, et al. 2014. Air concentrations of volatile compounds near oil and gas production: A community-based exploratory study. Environ Health 13:82-069X-13-82; doi: 10.1186/1476-069X-13-82.

Maloney KO, Yoxtheimer DA. 2012. Production and disposal of waste materials from gas and oil extraction from the Marcellus Shale play in Pennsylvania. Environ Practice 14(04):278-287.

Mitka M. 2012. Rigorous evidence slim for determining health risks from natural gas fracking. JAMA 307(20):2135-2136.

Patient-Reported Outcomes Measurement Information System. 2015. PROMIS Fatigue Short Form 8a. Available: http://www.assessmentcenter.net [accessed 10 October 2015].

New York State Department of Environmental Conservation. 2015. Final Supplemental Generic Environmental Impact Statement on the Oil, Gas, and Solution Mining Regulatory Program. Available: http://www.dec.ny.gov/docs/materials_minerals_pdf/fsgeis2015.pdf [accessed 10 October 2015].

Paulik LB, Donald CE, Smith BW, Tidwell LG, Hobbie KA, Kincl L, et al. 2015. Impact of natural gas extraction on PAH levels in ambient air. Environ Sci Technol 49(8):5203-5210.

Potter F. 1988. Survey of procedures to control extreme sampling weights. Proceeding of the Survey Research Methods Section of the American Statistical Association. Available: http://www.amstat.org/sections/srms/Proceedings/papers/1988_083.pdf [accessed 26 March 2016].

Powers M, Saberi P, Pepino R, Strupp E, Bugos E, Cannuscio CC. 2015. Popular epidemiology and "fracking": Citizens' concerns regarding the economic, environmental, health and social impacts of unconventional natural gas drilling operations. J Community Health 40(3):534-541.

Rabinowitz PM, Slizovskiy IB, Lamers V, Trufan SJ, Holford TR, Dziura JD, et al. 2015. Proximity to natural gas wells and reported health status: Results of a household survey in Washington county, Pennsylvania. Environ Health Perspect 123(1):21-26.

Ranjith G. 2005. Epidemiology of chronic fatigue syndrome. Occup Med 55(1):13-19.

Ricci JA, Chee E, Lorandeau AL, Berger J. 2007. Fatigue in the U.S. workforce: Prevalence and implications for lost productive work time. J Occup Environ Med 49(1):1-10.

Saberi P, Propert KJ, Powers M, Emmett E, Green-McKenzie J. 2014. Field survey of health perception and complaints of Pennsylvania residents in the Marcellus shale region. Int J Environ Res Public Health 11(6):6517-6527.

Sauro KM, Becker WJ. 2009. The stress and migraine interaction. Headache: The Journal of Head and Face Pain 49(9):1378-1386.

Shashy RG, Moore EJ, Weaver A. 2004. Prevalence of the chronic sinusitis diagnosis in Olmsted county, Minnesota. Arch Otolaryngol Head Neck Surg 130(3):320-323.

Sjostrand C, Savic I, Laudon-Meyer E, Hillert L, Lodin K, Waldenlind E. 2010. Migraine and olfactory stimuli. Curr Pain Headache Rep 14(3):244-251.

Steinzor N, Subra W, Sumi L. 2013. Investigating links between shale gas development and health impacts through a community survey project in Pennsylvania. New Solut 23(1):55-83.

Sundaresan AS, Hirsch AG, Storm M, Tan BK, Kennedy TL, Greene JS, et al. 2015. Occupational and environmental risk factors for chronic rhinosinusitis: A systematic review. Int Forum Allergy Rhinol; doi: 10.1002/alr.21573 [Online 16 June 2015].

Tan BK, Kern RC, Schleimer RP, Schwartz BS. 2013. Chronic rhinosinusitis: The unrecognized epidemic. Am J Respir Crit Care Med 188(11):1275-1277.

Townsend P. 1987. Deprivation. J Soc Policy 16(02):125-146.

Werner AK, Vink S, Watt K, Jagals P. 2015. Environmental health impacts of unconventional natural gas development: A review of the current strength of evidence. Sci Total Environ 505:1127-1141.

TABLES

Table 1. Comparison of selected characteristics in survey responders and non-responders.

	Responders (n = 7,785)	Non-responders (n = 15,525)	*p*-value
Continuous composite UNGD activity metric, mean (sd)	-0.02 (1.80)	0.01 (2.78)	0.26[a]
UNGD activity, n (%)			
Quartile 1	2052 (26.4)	3775 (24.3)	< 0.001[b]
Quartile 2	1828 (23.5)	3996 (25.7)	
Quartile 3	2017 (25.9)	3814 (24.6)	
Quartile 4	1888 (24.3)	3940 (25.4)	
Charlson index, mean (sd)	3.43 (2.76)	2.52 (2.65)	< 0.001[a]
Charlson index stratified by quartiles of UNGD activity, mean (sd)			
Quartile 1	3.27 (2.61)	2.46 (2.46)	
Quartile 2	3.37 (2.71)	2.48 (2.57)	NA
Quartile 3	3.61 (2.83)	2.68 (2.85)	
Quartile 4	3.47 (2.86)	2.48 (2.70)	
	$p < 0.001$[c]	$p < 0.001$[c]	

Abbreviations: UNGD, unconventional natural gas development; sd, standard deviation; NA, not applicable.

Patients who lived outside Pennsylvania were excluded (n = 390). UNGD activity was averaged over 90 days prior to the survey.

[a] *p*-value computed with *t*-test.

[b] *p*-value computed with chi-square test.

[c] Within responders and non-responders separately, *p*-values were computed with one-way analysis of variance (ANOVA) to compare mean Charlson index across quartiles of UNGD.

Environ Health Perspect DOI: 10.1289/EHP281
Advance Publication: Not Copyedited

Table 2: Characteristics of study population by self-reported outcome(s).

Characteristic	Overall study population	Individuals with no primary outcome		Individuals with one or more primary outcomes						
		Reference group[a]	Individuals who were neither cases nor controls[b]	Current CRS only	Migraine headache only	Higher levels of fatigue only	Current CRS and migraine	Current CRS and higher levels of fatigue	Migraine and higher levels of fatigue	Current CRS, migraine headache, and higher levels of fatigue
Total number, n	7785	1380	2889	738	580	666	268	347	420	497
Sex, n (%)										
Male	2909 (37.4)	656 (47.5)	1242 (43.0)	335 (45.4)	113 (19.5)	233 (35.0)	50 (18.7)	126 (36.3)	63 (15.0)	91 (18.3)
Female	4876 (62.6)	724 (52.5)	1647 (57.0)	403 (54.6)	467 (80.5)	433 (65.0)	218 (81.3)	221 (63.7)	357 (85.0)	406 (81.7)
Race/ethnicity, n (%)										
White non-Hispanic	7043 (90.5)	1183 (85.7)	2653 (91.8)	707 (95.8)	508 (87.6)	598 (89.8)	257 (95.9)	333 (96.0)	357 (85.0)	447 (89.9)
Other	742 (9.5)	197 (14.3)	236 (8.2)	31 (4.2)	72 (12.4)	68 (10.2)	11 (4.1)	14 (4.0)	63 (15.0)	50 (10.1)
Age in years, mean (sd)	55.3 (16.1)	58.8 (17.0)	57.6 (15.9)	57.1 (14.9)	46.1 (14.3)	57.3 (15.1)	48.5 (13.2)	56.1 (14.7)	46.5 (13.6)	47.8 (13.1)
Smoking status, n (%)										
Never	4268 (54.8)	805 (58.3)	1615 (55.9)	404 (54.7)	340 (58.6)	334 (50.2)	141 (52.6)	178 (51.3)	220 (52.4)	231 (46.5)
Current	1130 (14.5)	134 (9.7)	353 (12.2)	100 (13.6)	96 (16.6)	113 (17.0)	57 (21.3)	61 (17.6)	86 (20.5)	130 (26.2)
Former	2387 (30.7)	441 (32.0)	921 (31.9)	234 (31.7)	144 (24.8)	219 (32.9)	70 (26.1)	108 (31.1)	114 (27.1)	136 (27.4)
History of receiving Medical Assistance, n (%)										
Never	6876 (88.3)	1286 (93.2)	2690 (93.1)	694 (94.0)	467 (80.5)	588 (88.3)	216 (80.6)	293 (84.4)	302 (71.9)	340 (68.4)
Ever	909 (11.7)	94 (6.8)	199 (6.9)	44 (6.0)	113 (19.5)	78 (11.7)	52 (19.4)	54 (15.6)	118 (28.1)	157 (31.6)
Body mass index (kg/m^2), mean (sd)	30.2 (7.0)	29.0 (6.3)	29.9 (6.5)	30.4 (7.0)	29.7 (7.3)	31.7 (7.9)	29.8 (7.3)	31.3 (7.4)	31.7 (7.7)	31.2 (8.1)
Place type, n (%)										
Township	4949 (63.6)	907 (65.7)	1900 (65.8)	476 (64.5)	332 (57.2)	417 (62.6)	170 (63.4)	213 (61.4)	242 (57.6)	292 (58.8)
Borough	2135 (27.4)	371 (26.9)	762 (26.4)	188 (25.5)	183 (31.6)	192 (28.8)	72 (26.9)	101 (29.1)	122 (29.0)	144 (29.0)
Census tract in city	701 (9.0)	102 (7.4)	227 (7.9)	74 (10.0)	65 (11.2)	57 (8.6)	26 (9.7)	33 (9.5)	56 (13.3)	61 (12.3)
Community socioeconomic deprivation, mean (sd)	0.0 (3.6)	-0.3 (3.6)	-0.1 (3.6)	-0.1 (3.5)	0.3 (3.7)	0.1 (3.6)	0.2 (3.5)	0.1 (3.7)	0.6 (3.7)	0.6 (3.8)
UNGD activity metric, n (%)[c]										
Quartile 1 [-0.61 to -0.47]	1946 (25.0)	358 (25.9)	745 (25.8)	181 (24.5)	140 (24.1)	155 (23.3)	63 (23.5)	91 (26.2)	101 (24.0)	112 (22.5)
Quartile 2 [-0.47 to -0.39]	1946 (25.0)	345 (25.0)	731 (25.3)	187 (25.3)	145 (25.0)	174 (26.1)	65 (24.3)	83 (23.9)	92 (21.9)	124 (24.9)
Quartile 3 [-0.39 to -0.16]	1946 (25.0)	373 (27.0)	733 (25.4)	188 (25.5)	131 (22.6)	172 (25.8)	70 (26.1)	73 (21.0)	98 (23.3)	108 (21.7)
Quartile 4 [> -0.16]	1947 (25.0)	304 (22.0)	680 (23.5)	182 (24.7)	164 (28.3)	165 (24.8)	70 (26.1)	100 (28.8)	129 (30.7)	153 (30.8)

Abbreviations: CRS, chronic rhinosinusitis; UNGD, unconventional natural gas development; sd, standard deviation. Percentages may not total 100 due to rounding.

[a] Individuals in the reference group reported no past or current CRS; no headache-related nausea, photophobia, or disability; and lower levels ($\leq 25^{th}$ percentile) of fatigue.

[b] These individuals did not meet criteria for any primary outcome and were excluded from the reference group because of past CRS, intermediate probability of migraine headache, and/or moderate levels of fatigue.
[c] UNGD activity was averaged over the 90 days prior to the survey.

Table 3. Associations of UNGD with symptoms in individuals with one or more primary outcomes, compared to a reference group.

	Current CRS only (n = 736)[a]	Migraine headache only (n = 580)	Higher levels of fatigue only (n = 666)	Current CRS and migraine (n = 266)[a]	Current CRS and higher levels of fatigue (n = 347)[a]	Migraine and higher levels of fatigue (n = 420)	All three outcomes (n = 496)[a]
UNGD quartile	Adjusted odds ratios (95% confidence intervals)						
1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	1.17 (0.80, 1.72)	1.14 (0.74, 1.75)	1.48 (1.01, 2.17)	0.82 (0.43, 1.57)	1.06 (0.62, 1.80)	1.06 (0.63, 1.78)	1.05 (0.63, 1.78)
3	0.76 (0.52, 1.12)	0.89 (0.58, 1.36)	1.22 (0.84, 1.77)	0.74 (0.38, 1.47)	0.94 (0.53, 1.66)	0.80 (0.49, 1.31)	0.73 (0.42, 1.27)
4	1.11 (0.75, 1.65)	1.43 (0.94, 2.18)	1.47 (0.996, 2.18)	1.49 (0.78, 2.85)	1.88 (1.08, 3.25)	1.95 (1.18, 3.21)	1.84 (1.08, 3.14)

Abbreviations: UNGD, unconventional natural gas development; CRS, chronic rhinosinusitis.

For all models, the reference group consisted of individuals with no current or past CRS, no migraine headache symptoms, and the lowest quartile of fatigue score. All models included sampling weights, with the highest weight truncated to the value of second-highest weight. Models included these covariates: sex, race/ethnicity (white non-Hispanic vs. other), centered age (linear and quadratic terms), Medical Assistance (never vs. ever), and smoking status (never vs. current and former). UNGD activity was averaged over the 90 days prior to the survey.

[a] These models included centered body mass index as an additional covariate. Because individuals with unknown body mass index were excluded, these case counts are slightly lower than those reported in the text.

Table 4. Associations of UNGD with negative control outcomes.

	Ear pain yes (n = 422) vs. no (n = 3917)	Bad breath yes (n = 846) vs. no (n = 2628)	Cold/flu symptoms yes (n = 307) vs. no (n = 2442)
	Adjusted odds ratios (95% confidence intervals)		
UNGD quartile			
1	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	0.92 (0.58, 1.44)	0.87 (0.61, 1.22)	1.04 (0.58, 1.84)
3	0.53 (0.32, 0.87)	1.12 (0.80, 1.57)	1.15 (0.66, 2.00)
4	1.16 (0.74, 1.83)	0.95 (0.67, 1.35)	1.14 (0.64, 2.01)

Abbreviations: UNGD, unconventional natural gas development; CRS, chronic rhinosinusitis.

Individuals with the symptom at least “most of the time” in the past three months were compared to those with the symptom “never” in the past three months. All models included sampling and response weights, and the highest weight was truncated to the value of the second-highest weight. Models included these covariates: sex, race/ethnicity (white non-Hispanic vs. other), centered age (linear and quadratic terms), Medical Assistance (never vs. ever), and smoking status (never vs. current and former). UNGD activity was averaged over the 90 days prior to the survey.

FIGURE LEGENDS

Figure 1. Map of study area. Thick black outlines designate Pennsylvania counties with at least one participant (from U.S. Census Bureau TIGER/line files). Numbers within the borders of each county indicate the total number of participants (T) and the number with chronic rhinosinusitis symptoms (NS), migraine headache (H), and higher levels of fatigue (F) (data from the Geisinger Clinic). Gray circles show locations of drilled unconventional natural gas wells as of December 2014 (from Pennsylvania Department of Environmental Protection). Black stars represent Geisinger hospitals and clinics. Map was made with ArcGIS Desktop (release 10, Esri, Redlands, CA).

Figure 2. Locations of study participants in the fourth quartile of UNGD activity (**A**) and all other UNGD quartiles (**B**). Blue crosses: participants with at least one primary outcome (current CRS, migraine headache, and/or higher levels of fatigue). Black circles: reference group participants with no current or past CRS, no migraine headache symptoms, and lower levels of fatigue. Yellow circles: locations of all drilled unconventional natural gas wells in Pennsylvania as of December 31, 2014. Patient residential locations were from the Geisinger Clinic; county boundaries from the U.S. Census Bureau TIGER/line files; and UNGD wells from the Pennsylvania Department of Environmental Protection. Maps were made with ArcGIS Desktop (release 10, Esri, Redlands, CA).

Figure 1.

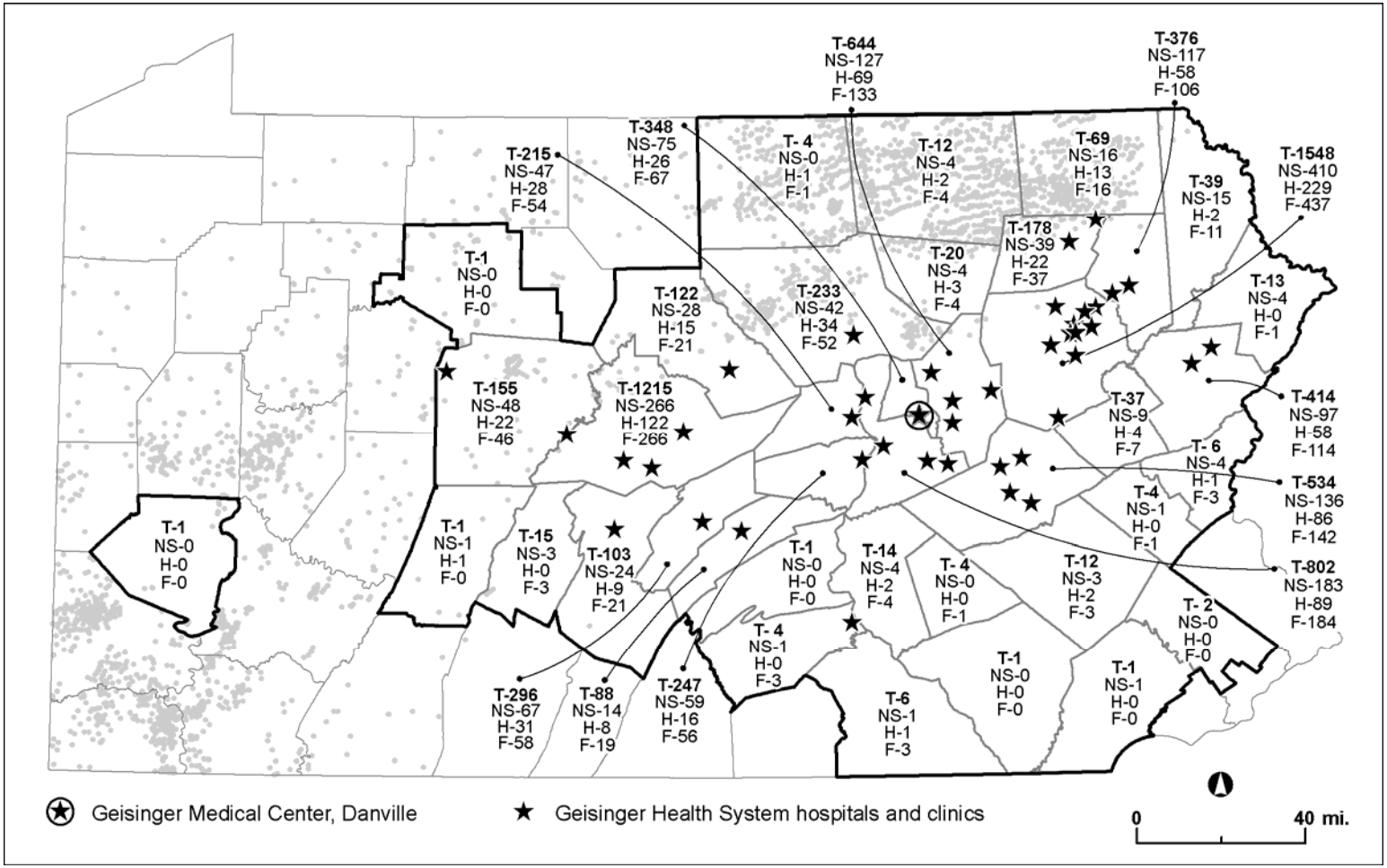
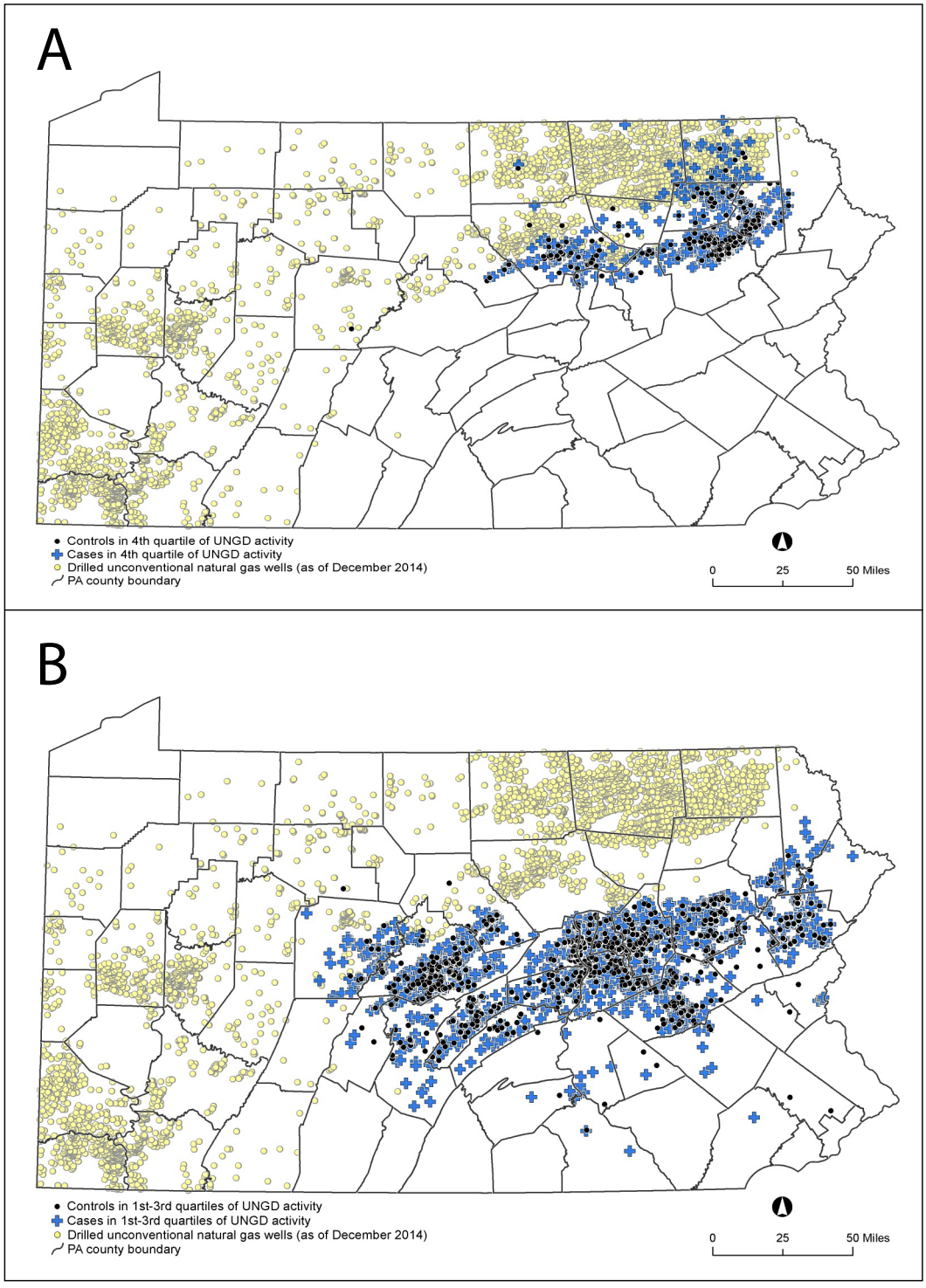

T-644
NS-127
H-69
F-133
T-376
NS-117
H-58
F-106
T-348
NS-75
H-26
F-67
T-215
NS-47
H-28
F-54
T- 4
NS-0
H-1
F-1
T-12
NS-4
H-2
F-4
T-69
NS-16
H-13
F-16
T-39
NS-15
H-2
F-11
T-1548
NS-410
H-229
F-437
T-178
NS-39
H-22
F-37
T-20
NS-4
H-3
F-4
T-1
NS-0
H-0
F-0
T-122
NS-28
H-15
F-21
T-233
NS-42
H-34
F-52
T-13
NS-4
H-0
F-1
T-155
NS-48
H-22
F-46
T-1215
NS-266
H-122
F-266
T-37
NS-9
H-4
F-7
T-414
NS-97
H-58
F-114
T- 6
NS-4
H-1
F-3
T-534
NS-136
H-86
F-142
T-4
NS-1
H-0
F-1
T-1
NS-0
H-0
F-0
T-1
NS-1
H-1
F-0
T-15
NS-3
H-0
F-3
T-103
NS-24
H-9
F-21
T-1
NS-0
H-0
F-0
T-14
NS-4
H-2
F-4
T- 4
NS-0
H-0
F-1
T-12
NS-3
H-2
F-3
T-802
NS-183
H-89
F-184
T- 2
NS-0
H-0
F-0
T- 4
NS-1
H-0
F-3
T-1
NS-0
H-0
F-0
T-1
NS-1
H-0
F-0
T-296
NS-67
H-31
F-58
T-88
NS-14
H-8
F-19
T-247
NS-59
H-16
F-56
T-6
NS-1
H-1
F-3
Geisinger Medical Center, Danville
Geisinger Health System hospitals and clinics
0
40 mi.

Figure 2.


A
Controls in 4th quartile of UNGD activity
Cases in 4th quartile of UNGD activity
Drilled unconventional natural gas wells (as of December 2014)
PA county boundary
0
25
50 Miles
B
Controls in 1st-3rd quartiles of UNGD activity
Cases in 1st-3rd quartiles of UNGD activity
Drilled unconventional natural gas wells (as of December 2014)
PA county boundary
0
25
50 Miles

OPEN ACCESS Freely available online

PLOS ONE

Early-Life Exposure to Polycyclic Aromatic Hydrocarbons and ADHD Behavior Problems

Frederica P. Perera[1,2]*, Hsin-wen Chang[2,3], Deliang Tang[1,2], Emily L. Roen[1,2], Julie Herbstman[1,2], Amy Margolis[2,4], Tzu-Jung Huang[2,3], Rachel L. Miller[1,2,5,6], Shuang Wang[2,3], Virginia Rauh[2,7]

1 Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **2** Columbia Center for Children's Environmental Health, Columbia University, New York, New York, United States of America, **3** Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **4** Division of Child & Adolescent Psychiatry and the Center for Developmental Neuropsychiatry, Department of Psychiatry, the New York State Psychiatric Institute and the College of Physicians and Surgeons, Columbia University, New York, New York, United States of America, **5** Division of Pulmonary, Allergy and Critical Care of Medicine, Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York, United States of America, **6** Division of Pediatric Allergy and Immunology, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, New York, United States of America, **7** The Heilbrunn Department of Population and Family Health, Columbia University, New York, New York, United States of America

Abstract

Importance: Polycyclic aromatic hydrocarbons are widespread urban air pollutants from combustion of fossil fuel and other organic material shown previously to be neurotoxic.

Objective: In a prospective cohort study, we evaluated the relationship between Attention Deficit Hyperactivity Disorder behavior problems and prenatal polycyclic aromatic hydrocarbon exposure, adjusting for postnatal exposure.

Materials and Methods: Children of nonsmoking African-American and Dominican women in New York City were followed from *in utero* to 9 years. Prenatal polycyclic aromatic hydrocarbon exposure was estimated by levels of polycyclic aromatic hydrocarbon- DNA adducts in maternal and cord blood collected at delivery. Postnatal exposure was estimated by the concentration of urinary polycyclic aromatic hydrocarbon metabolites at ages 3 or 5. Attention Deficit Hyperactivity Disorder behavior problems were assessed using the Child Behavior Checklist and the Conners Parent Rating Scale- Revised.

Results: High prenatal adduct exposure, measured by elevated maternal adducts was significantly associated with all Conners Parent Rating Scale-Revised subscales when the raw scores were analyzed continuously (N = 233). After dichotomizing at the threshold for moderately to markedly atypical symptoms, high maternal adducts were significantly associated with the Conners Parent Rating Scale-Revised DSM-IV Inattentive (OR = 5.06, 95% CI [1.43, 17.93]) and DSM-IV Total (OR = 3.37, 95% CI [1.10, 10.34]) subscales. High maternal adducts were positivity associated with the DSM-oriented Attention Deficit/Hyperactivity Problems scale on the Child Behavior Checklist, albeit not significant. In the smaller sample with cord adducts, the associations between outcomes and high cord adduct exposure were not statistically significant (N = 162).

Conclusion: The results suggest that exposure to polycyclic aromatic hydrocarbons encountered in New York City air may play a role in childhood Attention Deficit Hyperactivity Disorder behavior problems.

Citation: Perera FP, Chang H-w, Tang D, Roen EL, Herbstman J, et al. (2014) Early-Life Exposure to Polycyclic Aromatic Hydrocarbons and ADHD Behavior Problems. PLoS ONE 9(11): e111670. doi:10.1371/journal.pone.0111670

Editor: Robert L. Tanguay, Oregon State University, United States of America

Received June 5, 2014; **Accepted** October 6, 2014; **Published** November 5, 2014

Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. The data on which the manuscript is based are not freely available in the manuscript, supplemental files, or in a public repository, although a de-identified dataset is available upon request. Requests for data should be submitted to the corresponding author, Dr. Frederica Perera, fpp1@columbia.edu. The data are not freely available because they contain a significant number of data elements that are considered Protected Health Information (PHI) under HIPAA regulations. We will make the data available upon request as a Limited Data Set, under a standard HIPAA Data Use Agreement that will be reviewed and approved by our Columbia University Privacy Officer.

Funding: Funding was provided by the National Institute for Environmental Health Sciences (NIEHS) and the U.S. Environmental Protection Agency (US EPA): NIEHS/EPA P01ES09600/R82702701, NIEHS/EPA P01ES09600/RD832141, NIEHS/EPA P01ES09600/RD834509, NIEHS R01ES08977. This publication was also made possible in part by US EPA grants RD832096, the John & Wendy Neu Family Foundation, the New York Community Trust, Trustees of the Blanchette Hooker Rockefeller Fund, and an anonymous foundation. Funding from all the institutions listed was used towards the design and conduct of the study; collection, management, analysis, and interpretation of the data; and the preparation, review, and approval of the manuscript. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the US EPA. Further, US EPA does not endorse the purchase of any commercial products or services mentioned in the publication. Findings expressed in this paper are the opinions of the authors and do not necessarily reflect the official opinion of the Centers for Disease Control and Prevention.

Competing Interests: The authors have declared that no competing interests exist.

* Email: fpp1@columbia.edu

Introduction

Polycyclic aromatic hydrocarbons (PAH), such as benzo[a]pyrene (B[a]P), are toxic air pollutants released during incomplete combustion of fossil fuel, tobacco, and other organic material [1]. They are also found in the diet. In New York City (NYC) and other urban areas, traffic and residential heating are major local sources. There is also some contribution from coal-burning sources in states upwind. Urban, minority populations in the U.S. often have disproportionate exposure to air pollution and are at greater risk for adverse health and developmental outcomes from this exposure [2–5]. All of the mothers in the Columbia Center for Children's Environmental Health (CCCEH) NYC cohort had detectable levels of PAH in prenatal personal air samples; 42% had detectable levels of B[a]P-DNA adducts in maternal blood; and 46% had detectable levels of B[a]P-DNA adducts in cord blood. B[a]P is considered a representative PAH and is highly correlated with other PAH class members [6]. PAH-DNA adducts reflect individual exposure to PAH, integrating exposure over a 2–3 month period [7]and via different routes (primarily inhalation and ingestion). Adducts provide a biologic dosimeter as they not only reflect inter-individual differences in exposure and uptake of PAH but also in detoxification and DNA repair [8,9].

Because of the heightened susceptibility of the fetus and young child, exposures to PAH and other environmental pollutants during the prenatal and early postnatal stages are of particular concern [10–13]. During the fetal period and early childhood years, the brain is rapidly developing and vulnerable to neurotoxic insults that may manifest as adverse outcomes in childhood and adulthood [14,15]. Laboratory studies of PAH exposure during the prenatal, neonatal, or adult periods have reported a range of neurodevelopmental and behavioral effects, [16,17] including hyperactivity [18,19]. In the present CCCEH cohort, prenatal exposure to PAH measured by prenatal air monitoring or B[a]P-DNA adducts in maternal or umbilical cord blood at delivery was associated with developmental delay at age 3 [20], reduced IQ at age 5 [21], and symptoms of anxiety/depression and attention problems at ages 6–7 [6].

Attention-deficit/hyperactivity disorder (ADHD) is the most common behavioral disorder diagnosed in children [22] and is often accompanied by anxiety and depression [23–26]. In our cohort, ADHD behavior problems and anxiety/depression at age 9 were significantly correlated ($r = 0.43$, $p<0.0001$). Children with ADHD are at increased risk of substance abuse, conduct, and mood disorders [27–30]. Family history, certain environmental contaminants, alcohol use, maternal smoking during pregnancy, pregnancy and delivery complications, and psychosocial adversity have been implicated or identified as risk factors for ADHD [31,32].

Prior data on air pollution and ADHD are suggestive. For example, a cross-sectional study found an association between ambient particulate matter (PM_{10}) and childhood ADHD [33]. In a longitudinal study, estimated exposure during infancy to elemental black carbon, based on air sampling data and land use regression modeling, was significantly associated with ADHD-related symptoms [34]. Another cohort study reported an association between attention and children's lifetime exposure to black carbon based on children's residence and a spatiotemporal model [35]. Ours is the first report of associations between individual measures of early-life exposure to PAH pollutants and ADHD behavior problems in children.

Methods

Sample selection

A complete description of the NYC cohort appears elsewhere [20,36]. Briefly, African-American and Dominican women who resided in Washington Heights, Harlem, or the South Bronx in NYC, U.S., were recruited between 1998 and 2006 through local prenatal care clinics. Enrollment was restricted to women who were non-active cigarette smokers; ages 18–35; non-users of other tobacco products or illicit drugs; free of diabetes, hypertension, or known HIV; and who had initiated prenatal care by the 20th week of pregnancy. The Institutional Review Board of the Columbia University Medical Center approved the study. Mothers signed a consent form, approved by the IRB, for themselves and their children at the time of enrollment and at every subsequent visit. The children sign an IRB-approved assent form beginning at age 7. The consent and assent forms are available in English and Spanish and clearly explain the study goals and procedures.

The sample included in the present analysis is composed of the children who had available data on at least one adduct measure (maternal or newborn), the CPRS and the CBCL assessments, and all covariates of interest ($N = 250$).

Maternal/child characteristics and home caretaking environment

Demographic, health and environmental conditions. A 45-minute structured questionnaire was administered by a trained bilingual interviewer during the last trimester of pregnancy to obtain demographic information, residential history, and health and environmental data such as active smoking (to confirm non-active smoking status) and passive smoking [36]. The questionnaire also elicited information on dietary PAH (consumption of broiled, fried, grilled or smoked meat), and socioeconomic information related to income and education. Postnatal interviews were administered in person at 6 months and annually thereafter to determine changes in residence, exposure to environmental tobacco smoke (ETS), and health and environmental conditions.

Maternal demoralization. Maternal demoralization, a measure of maternal nonspecific psychological distress that has been linked to neurodevelopment [37–39], was measured at each visit by the Psychiatric Epidemiologic Research Instrument Demoralization Scale (PERI-D) [40].

Non-verbal intelligence. The Test of Non-Verbal Intelligence-Second Edition (C-TONI-2) [41] was administered to the mothers when the child was about 3 years old.

Home assessment. Caldwell and Bradley's Home Observation for Measurement of the Environment (HOME) [42] was administered in the home by research workers, also when the child was about 3 years old, to assess physical and interactive characteristics of the child rearing environment.

Maternal ADHD. At the child's 7 year visit, mothers completed the Conners Adult ADHD Rating Scales (CAARS) [43]. Given the high heritability rate of ADHD [44], maternal ADHD symptoms on the CAARS were included as a covariate in our analyses.

Child anxiety/depression. Childhood ADHD and anxiety/depression are frequently comorbid conditions [24]. The continuous score for symptoms of anxiety/depression on the CBCL at age 9 [45] was included as a covariate.

Independent variables

Prenatal exposure: PAH-DNA adducts. Following delivery, maternal blood and umbilical cord blood samples were collected. Within several hours following collection, samples were

transported to the CCCEH Molecular Epidemiology Laboratory, processed, and stored at −70°C. B[a]P–DNA adducts in extracted white blood cell DNA were analyzed using the high performance liquid chromatography (HPLC)/fluorescence method which detects B[a]P tetraols [12,46]. Not all participants had adequate DNA quantity for adduct analysis.

Postnatal exposure: urinary PAH metabolites. At the CDC, a suite of PAH metabolites was measured in spot urine (collected from the child at ages 3 and 5) using automated liquid-liquid extraction and gas chromatography/isotope dilution high-resolution mass spectrometry [47–49]. Although PAH urinary metabolite have a short lifetime (half-life of 6–35 hours) [50], in conditions of chronic exposure they provide a useful measure of exposure to PAH [47,48]. Specific gravity (SG) measurements were used to control for urinary dilution of the samples using the following formula: freshweight metabolites for the subject*(mean SG-1)/(SG for that subject-1) [51,52].

Behavioral outcomes

ADHD behavior problems were assessed using two complementary parent-report instruments: the CBCL for ages 6–18 (CBCL) [53] and the CPRS- Revised: Long Version [54]. The CBCL is a screening instrument assessing childhood competencies, adaptive functioning, and problems [45]. The CPRS is a focused assessment of childhood ADHD and its common comorbid disorders [54,55]. Both are widely used instruments that measure ADHD problems and attention function and have been used to study their associations with diverse environmental contaminants [56–59]. Both instruments yield scales derived from the DSM-IV [60] that are intended to screen for ADHD-behavior problems and indicate those children requiring follow-up. Mothers self-administered the 80-item CPRS [54] and the 118-item CBCL [53] when their children were 9 years old, under the guidance of trained research workers. Outcomes analyzed included the CBCL DSM-oriented Attention Deficit/Hyperactivity Problems scale, and the CPRS ADHD Index and DSM-IV subscales (denoted as "Total", "Inattentive", and "Hyperactive-Impulsive"). The "Total" DSM-IV measure comprises the "Inattentive" and "Hyperactive-Impulsive" subscales. For both instruments, the child's responses were scored and summed to a raw score. T-scores were derived from raw scores based on the normative comparison sample as described in the administration manual and used to determine the child's classification [53,54]. On the CBCL DSM-oriented Attention Deficit/Hyperactivity Problems score, children above the 93rd percentile were classified as "borderline clinical", and those below the 93rd percentile were classified in the normal range [53]. The CPRS DSM-IV subscales and ADHD Index scores were dichotomized based on the classification of a T score >65 as "moderately to markedly atypical" and a T score ≤65 as "in the normal range" [54].

Statistical Analysis

As in prior analyses [6], adduct levels were dichotomized as detectable/non-detectable ("high/low"), with detectable levels observed in 42% of maternal and 46% of cord blood samples in the whole cohort. Dichotomization of exposure variables is less vulnerable to measurement error and permits comparison of the most highly exposed children to children with lower exposure. In our analyses, (1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene) were summed to provide a composite measure denoted "PAH metabolites". PAH metabolites in child urine at ages 3 or 5 were dichotomized at the respective medians for the entire cohort and treated as "high/low". In terms of data analysis, the age 5 metabolite level was preferentially selected, but if that measure was missing, the age 3 metabolite level was used. In secondary analyses, adducts and PAH metabolites were also treated as a continuous variable after log transformation.

Covariates were selected based on whether they were significant contributors to the model (at $p \leq 0.1$) for at least one of the outcomes and included: prenatal ETS exposure, child's sex, child's ethnicity, child's gestational age, mother's intelligence, mother's completed years of education prior to birth of the child, maternal prenatal demoralization, maternal ADHD symptoms, child's exact age at assessment (in months), the quality of the early home caretaking environment, and season at time of monitoring (heating vs. non-heating) (Table 1). We further adjusted for child anxiety/depression at age 9 since it is a well-documented comorbid condition with ADHD and symptoms overlap [24]. Moreover, we have previously found associations of PAH with child anxiety/depressive symptoms [6]. Dietary PAH, measured prenatally during the third trimester, was not a predictor of outcomes at $p \leq 0.1$. The associations between the dichotomized PAH exposure variables and continuous raw scores and dichotomized T scores for ADHD-related behavior were analyzed by Poisson and logistic regression, respectively.

Results

Maternal and cord adducts were not significantly correlated with prenatally air monitored PAH, ETS, or dietary PAH.

Table 1 presents the socio-demographic, outcome, and exposure characteristics of the children who had available data on maternal or cord adducts, stratifying on whether or not they had data on neurobehavioral outcomes and covariates of interest and were thus included (N = 250) or not included (N = 364) in the analysis. The two groups were similar except that the group included had a higher proportion of females and were younger at the CPRS assessment, though all assessments were given at approximately age 9. The level of adducts and percentage characterized as high vs. low did not differ between those included and not included. Comparing the group included (N = 250) with those children who did not have maternal or cord adduct data (N = 111), there were differences in terms of exact age at assessment for the CBCL and CPRS, home inventory scores, and percentage of mothers that had completed high school (data not shown).

Table 2 summarizes the distribution of CBCL and CPRS scores in the entire sample. Table 3 shows the number of children in the borderline or clinical range on the CBCL, and the number in the moderately to markedly atypical range on the CPRS. Consistent with other studies, there was substantial overlap between the number of children categorized in the moderately to markedly atypical range on the Hyperactive-Impulsive and Inattentive problems, as shown in Figure 1.

Table 4 summarizes the associations between maternal (N = 233) and cord adduct (N = 162) exposure and CBCL DSM-oriented Attention Deficit/Hyperactivity problems and all CPRS outcomes, adjusting for postnatal PAH exposure and selected covariates. When considering outcomes analyzed as continuous raw scores, all CPRS subscales were positively and significantly associated with high maternal adduct exposure. After dichotomizing the outcome measures, those with high maternal adducts had odds of being categorized as moderately to markedly atypical on the DSM-IV Inattentive and DSM-IV Total scales 5.06 (95% CI [1.43, 17.93]) and 3.37 (95% CI [1.10, 10.34]) times greater than those with low maternal adducts. High maternal adduct exposure

Table 1. Characteristics of the children included in the analysis and those not included due to missing data.

	Subjects included in the analysis (N = 250)[a]	Subjects not included in the analysis (N = 364)[b]	
Variables	Mean ±SD or %	Mean ±SD or %	p-value
High maternal adducts[c]	37.34%	44.25%	0.10
High cord adducts[c]	39.51%	49. 37%	0.07
High urinary PAH metabolites at ages 3 or 5[d]	49.20%	55.07%	0.22
Log-transformed urinary PAH metabolites at ages 3 or 5[e]	9.02±0.89	9.03±0.80	0.86
Log-transformed maternal adduct (per 10^8 nucleotides)	−1.73±0.47	−1.68±0.48	0.20
Log-transformed cord adduct (per 10^8 nucleotides)	−1.67±0.53	−1.59±0.53	0.13
CBCL DSM-oriented Attention Deficit/Hyperactivity Problems (% with borderline or clinical diagnosis)[f]	7.20%	10.66%	0.32
CPRS subscales (% categorized as moderately to markedly atypical)[g]			
ADHD Index	8.40%	7.87%	1.00
DSM-IV Inattentive	8.40%	5.51%	0.41
DSM- IV Hyperactive- Impulsive	10.80%	14.17%	0.40
DSM-IV Total	10.40%	7.87%	0.47
Prenatal ETS exposure (% yes)	33.20%	37.36%	0.30
Child sex (% female)	**57.60%**	**48.35%**	**0.03***
Child ethnicity (AA%)[h]	40.00%	33.24%	0.09
Gestational age (in weeks)[i]	39.35±1.37	39.34±1.44	0.94
Maternal intelligence[j]	20.82±8.78	20.25±8.62	0.47
Maternal education (%≥ high school education)	64.80%	59.83%	0.24
Maternal demoralization score	1.15±0.61	1.18±0.67	0.67
Maternal ADHD (CAARS ADHD index raw score)[k]	38.79±8.87	37.67±7.16	0.15
CBCL age (in months)[l]	108.01±1.83	108.78±4.60	0.14
CPRS age (in months)[l]	**107.96±2.02**	**109.15±4.97**	**0.03***
Home environment[m]	40.09±5.94	39.33±6.09	0.18
Heating season (% yes)[n]	54.0%	56.52%	0.64
Child anxiety/depression (CBCL anxiety/depression raw score)[o]	2.74±3.02	2.53±2.80	0.53

[a]Subjects were included if they had data for maternal adducts and/or cord adducts, as well as data on CBCL, CPRS outcome and all covariates of interest.
[b]Subjects not included are those that had available data on cord and/or maternal adducts but were missing data on the CBCL, CPRS outcomes and/or any covariates included in the final model.
[c]Adduct levels were dichotomized as detectable/non-detectable (''high/low'').
[d]PAH metabolites in child urine at ages 3 or 5 were dichotomized at the respective medians (''high/low'').
[e]Children with urinary PAH metabolite measurement at ages 3 or 5.
[f]Based on T score. Borderline or clinical defined as percentile ≥93rd.
[g]Based on T score. Moderately to markedly atypical defined as T-score >65.
[h]Percent African American; the remainder are Dominican.
[i]Based on medical record data.
[j]Nonverbal intelligence measured by the TONI-2.
[k]Measure of maternal ADHD.
[l]Age at administration.
[m]HOME Inventory as a measure of the home caretaking environment.
[n]Third trimester in heating season.
[o]Based on CBCL Anxious/Depressed Syndrome Scale measured at age 9.
*p-value <0.05.
doi:10.1371/journal.pone.0111670.t001

was also significantly and positively associated with the CDCL DSM-oriented Attention Deficit/Hyperactivity Problems scale, though results did not reach statistical significance.

In separate models with log transformed adduct and metabolite values as the exposure variables, the direction and significance of the associations between adducts and outcomes were the same as the models with the dichotomized exposure with the exception of the CBCL DSM-oriented attention deficit hyperactivity scale raw score and CPRS DSM-IV Total scale raw score, which became borderline significant ($p = 0.06$, and $p = 0.08$, respectively) (data not shown).

Parallel analyses in the smaller number of subjects with available cord adduct data (N = 162) exposure found non-significant or borderline significant associations with all outcomes (Table 4).

Discussion

The present results suggest that high prenatal exposure, taking into account the potential effects of postnatal PAH exposure, may

Table 2. Distribution of CBCL and CPRS Scores in children at age 9 (N = 250[a]).

	Score Range		Mean of Scores		Percent in Borderline or clinical or Moderately to markedly atypical range[b]
Outcomes	**T Score**	**Raw Score**	**T score**	**Raw score**	
CBCL DSM-oriented Attention Deficit/ Hyperactivity Problems	50–80	0–14	53.9	3.1	7.2
CPRS subscales					
ADHD Index	40–89	0–34	49.8	6.4	8.4
DSM-IV Total	40–90	0–48	50.8	9.2	10.4
DSM-IV Hyperactive- Impulsive	41–90	0–25	52.8	4.7	10.8
DSM-IV Inattentive	40–88	0–25	48.9	4.5	8.4

[a]Children included in analysis with all covariates.
[b]CBCL "borderline or clinical" defined as percentile ≥93rd; CPRS "moderately to markedly atypical" defined as T-score >65.
doi:10.1371/journal.pone.0111670.t002

increase the risk of ADHD behavior problems. ADHD is a disorder that is known to impact school performance, social relationships, and occupational performance [61–66]. In the U.S. the annual societal cost of illness for ADHD is estimated to be between $36 and $52 billion, and the annual cost per individual is estimated to be $12,005 to $17,458 (2005) [67,68].

To our knowledge, there have been no prior epidemiological studies on the role of pre- and post-natal PAH exposure, here measured by chemical-specific biomarkers, on ADHD in school-age children. Prior experimental research and limited epidemiological studies have suggested links between PM and air pollution (elemental carbon and black carbon) and ADHD symptoms [33–35]. In the present longitudinal study high maternal adduct levels were not significantly associated with Attention Deficit/Hyperactivity problems on the CBCL screening test, but on the more detailed CPRS, consistently significant associations with a number of ADHD-related outcomes were seen. In particular, significant associations between high maternal adducts and the DSM-IV Total and DSM-IV Inattentive scales were observed in models treating CPRS scores as continuous and dichotomous outcomes. Consistency in the results across both of these outcome measures strengthens the conclusion that inattention is associated with prenatal PAH exposure.

The maternal and cord adducts were significantly but only modestly correlated ($r = 0.28$, $p < 0.0001$), probably because of the immaturity of the metabolic/detoxification and DNA repair systems in the fetus compared to the adult [69] and the differing genetic profiles of the mother and the child. The stronger relationship between the maternal adducts and ADHD-related outcomes than between the cord adducts and the same outcomes could be attributable to the effects of exposure on placental function and/or the fact that high levels of maternal adducts indicate that the mother has been highly exposed and is an efficient activator of PAH, resulting in higher transplacental exposure to reactive PAH intermediates. We used urinary PAH metabolites to assess postnatal exposure. This biomarker has been employed in many studies as an indicator of PAH exposure in the general population [70]. Although they represent recent exposure [71], the metabolites can provide a chronic measure of ambient PAH in populations with constant exposure [72].

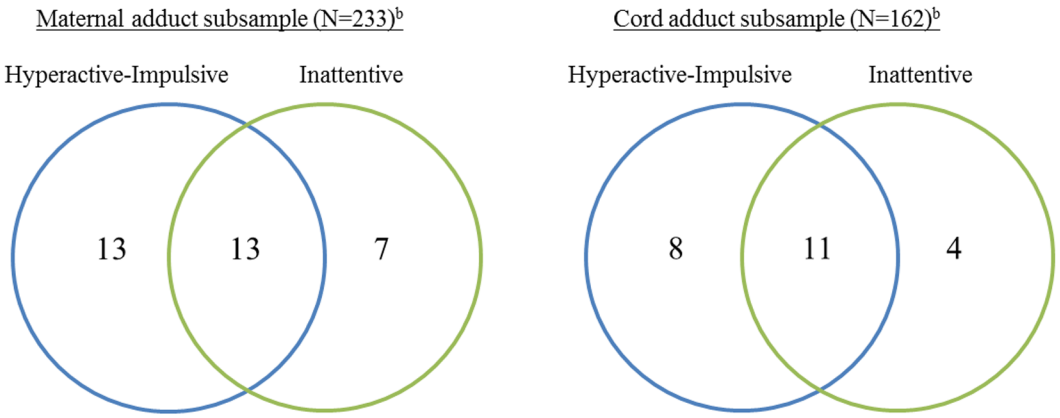
The mechanisms by which PAH exposure might affect the developing brain are not fully understood. Several pathways have been suggested including endocrine disruption [73–75], binding to receptors for placental growth factors resulting in decreased exchange of oxygen and nutrients [76], binding to the human Ah receptor to induce P450 enzymes [77], DNA damage resulting in activation of apoptotic pathways [78–80], oxidative stress due to inhibition of the brain antioxidant scavenging system [81], and epigenetic alterations [82]. The prenatal period is critical because of the extensive structural and cellular-level changes that occur during this stage of development. However, because brain development and growth occurs throughout childhood, postnatal exposures to environmental pollutants may also affect children's neurodevelopment and behavior [83].

The strengths of the study include our ability to account for a number of potential confounding variables and to draw upon

Table 3. Number of children scoring in the borderline or clinical range on the CBCL and in the moderately to markedly atypical range on the CPRS in the analyses with maternal adducts or cord adducts[a].

	Maternal Adducts (N = 233)	Cord Adducts (N = 162)
CBCL DSM-oriented Attention Deficit/Hyperactivity Problems (Borderline or clinical[b])	18	15
CPRS subscales (Moderately to markedly atypical[b])		
ADHD Index	20	14
DSM-IV Total	25	19
DSM-IV Hyperactive Impulsive	26	19
DSM-IV Inattentive	20	15

[a]Children included in analysis with all covariates.
[b]CBCL- Borderline or clinical defined as percentile ≥93rd; CPRS- Moderately to markedly atypical defined as T-score >65.
doi:10.1371/journal.pone.0111670.t003



[a] CBCL- Borderline or clinical defined as percentile > 93rd; CPRS- Moderately to markedly atypical defined as T-score >65
[b] Children included in analysis with all covariates

Figure 1. Number of children categorized as moderately to markedly atypical on the CPRS DSM-IV Hyperactive Impulsive and CPRS DSM-IV Inattentive Subscales[a].
doi:10.1371/journal.pone.0111670.g001

individual pre- and post-natal exposure data from biomarker and questionnaire data. We were able to use two complementary age-appropriate instruments to measure ADHD–related behaviors. The CBCL screens for various childhood behavior problems, including ADHD [53]. The CPRS tests specifically for ADHD and related problem behaviors and is intended to be more diagnostic than the CBCL [54]. Due to the prospective nature of our cohort study we were able to assess the association between environmental exposures sustained prenatally and future development of ADHD-related behaviors in childhood.

A limitation of the study is that unmeasured factors such as other pollutants, stress, and noise may have contributed to residual confounding. In addition, the number of children with moderately to markedly atypical outcomes on the CPRS (cases) was small, resulting in fairly wide confidence intervals around the odds ratios. However, the confidence intervals around the effect estimates for the continuous outcomes are much tighter. Although of interest, we

Table 4. Associations between PAH Exposure and CBCL DSM-oriented Attention Deficit/Hyperactivity problems and ADHD Behavior Problems on the CPRS Subscales adjusting for postnatal exposure[a].

	Maternal Adduct (N = 233)	Cord Adduct (N = 162)
Outcomes analyzed continuously		
	$\beta_{adducts}$(95% CI[b])	$\beta_{adducts}$ (95% CI[b])
CBCL DSM-oriented Attention Deficit/Hyperactivity Problems	0.13 (−0.03, 0.29)	−0.04 (−0.23, 0.15)
CPRS subscales		
ADHD Index	**0.14 (0.03, 0.25)***	−0.06 (−0.19, 0.07)
DSM-IV Total	**0.16 (0.07, 0.26)***	0.009 (−0.10, 0.12)
DSM-IV Hyperactive-Impulsive	**0.16 (0.03, 0.29)***	0.10 (−0.05, 0.26)
DSM-IV Inattentive	**0.17 (0.04, 0.31)***	−0.09 (−0.25, 0.06)
Outcomes analyzed dichotomously[c]		
	OR[b] (95% CI[b])	OR[b] (95% CI[b])
CBCL DSM-oriented Attention Deficit/Hyperactivity Problems	1.48 (0.38, 5.79)	1.17 (0.24, 5.66)
CPRS subscales		
ADHD Index	1.83 (0.61, 5.54)	0.93 (0.22, 4.01)
DSM-IV Total	**3.37 (1.10, 10.34)***	1.70 (0.47, 6.17)
DSM-IV Hyperactive-Impulsive	1.58 (0.55, 4.52)	1.04 (0.30, 3.61)
DSM-IV Inattentive	**5.06 (1.43, 17.93)***	1.32 (0.31, 5.56)

[a]Adjusting for postnatal PAH exposure (measured by metabolites at ages 3 or 5, adjusted for specific gravity), prenatal ETS, child sex, maternal education, child ethnicity, gestational age, maternal demoralization, heating season, HOME caretaking environment, maternal intelligence, child age at assessment, maternal ADHD, child anxiety/depression at age 9.
[b]OR stands for odds Ratio; CI stands for Confidence Interval.
[c]CBCL- Borderline or clinical defined as percentile ≥93rd; CPRS- Moderately to markedly atypical defined as T-score >65.
*p-value <0.05.
doi:10.1371/journal.pone.0111670.t004

did not have complete data on exposure to lead or mercury and were unable to account for this in our models. We were also unable to evaluate the effects of individual postnatal PAH metabolites that may have differing toxicities; however benzo[a]pyrene is an important, toxic member of the class of PAH. Finally, generalizability was reduced by the ethnicity restriction of our cohort (African-American and Dominican) and our exclusion of active smokers, illicit drug users, and women with pre-existing disease.

Conclusions

In conclusion, this study provides evidence that early exposure to environmental PAH may contribute to ADHD behavior problems in children. The results require confirmation but are of concern since children with ADHD are at greater risk of risk-taking behaviors [84], poor academic performance [85], and lower earnings in adulthood [86,87]. ADHD imposes large costs on society, estimated to range between $36 billion and $52 billion annually [67,68].

PAH are widespread in urban environments worldwide largely as a result of fossil fuel combustion. Fortunately, it is possible to reduce airborne PAH concentrations using currently available pollution controls, greater energy efficiency, the use of alternative energy sources, and regulatory intervention to control polluting sources.

Acknowledgments

Funding was provided by the National Institute for Environmental Health Sciences (NIEHS) and the U.S. Environmental Protection Agency (US EPA): NIEHS/EPA P01ES09600/R82702701, NIEHS/EPA P01ES09600/RD832141, NIEHS/EPA P01ES09600/RD834509, NIEHS R01ES08977. This publication was also made possible in part by US EPA grants RD832096, the John & Wendy Neu Family Foundation, the New York Community Trust, Trustees of the Blanchette Hooker Rockefeller Fund, and an anonymous foundation. Funding from all the institutions listed was used towards the design and conduct of the study; collection, management, analysis, and interpretation of the data; and the preparation, review, and approval of the manuscript. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the US EPA. Further, US EPA does not endorse the purchase of any commercial products or services mentioned in the publication. Findings expressed in this paper are the opinions of the authors and do not necessarily reflect the official opinion of the Centers for Disease Control and Prevention.

Analysis of PAH metabolites was conducted at the Centers for Disease Control and Prevention, National Center for Environmental Health, Division of Laboratory Sciences, 4770 Buford Highway, Atlanta, Georgia 30341, United States, in the laboratory of Andreas Sjodin, PhD. We also thank Joanne Chin, MFA, at the Columbia Center for Children's Environmental Health, 722 W. 168th Street, New York, NY 10032, United States, for assistance in manuscript preparation.

Author Contributions

Acquired the data: FPP HC AM TH SW VR. Interpreted the data: FPP HC AM TH SW VR. Drafted the article or revised it critically for important intellectual content: FPP ELR AM SW VR. Final approval of the version to be published: FPP HC DT ELR JH RLM AM TH SW VR.

References

1. Bostrom CE, Gerde P, Hanberg A, Jernstrom B, Johansson C, et al. (2002) Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environ Health Perspect 110: 451–488.
2. Perera FP, Illman SM, Kinney PL, Whyatt RM, Kelvin EA, et al. (2002) The challenge of preventing environmentally related disease in young children: community-based research in New York City. Environ Health Perspect 110: 197–204.
3. Woodruff TJ, Parker JD, Kyle AD, Schoendorf KC (2003) Disparities in exposure to air pollution during pregnancy. Environmental Health Perspectives 111: 942–946.
4. Jerrett M (2009) Global Geographies of Injustice in Traffic-Related Air Pollution Exposure. Epidemiology 20: 231–233 210.1097/EDE.1090b1013e318197 76a31819771.
5. Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD (2011) Understanding The Cumulative Impacts Of Inequalities In Environmental Health: Implications For Policy. Health Affairs 30: 879–887.
6. Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, et al. (2012) Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at age 6–7. Environ Health Perspect.
7. Mooney LA, Santella RM, Covey L, Jeffrey AM, Bigbee W, et al. (1995) Decline of DNA damage and other biomarkers in peripheral blood following smoking cessation. Cancer Epidemiol Biomarkers Prev 4: 627–634.
8. Godschalk RWL, Van Schooten FJ, Bartsch H (2003) A critical evaluation of DNA adducts as biological markers for human exposure to polycyclic aromatic compounds. Journal of Biochemistry and Molecular Biology 36: 1–11.
9. Veglia F, Loft S, Matullo G, Peluso M, Munnia A, et al. (2008) DNA adducts and cancer risk in prospective studies: a pooled analysis and a meta-analysis. Carcinogenesis 29: 932–936.
10. Anderson LM, Diwan BA, Fear NT, Roman E (2000) Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ Health Perspect 108: 573–594.
11. National Research Council (1993) Toxicity Testing and Strategies to Determine Needs and Priorities. Washington, D.C.: National Academy Press.
12. Perera FP, Tang D, Jedrychowski W, Hemminki K, Santella RM, et al. (2004) Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage. Environ Health Perspect 112: 1133–1136.
13. Grandjean P, Landrigan PJ (2006) Developmental neurotoxicity of industrial chemicals. Lancet 368: 2167–2178.
14. Stein J, Schettler T, Wallinga D, Valenti M (2002) In harm's way: toxic threats to child development. J Dev Behav Pediatr 23: S13–22.
15. Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of Child And Family Health, Committee on Early Childhood, Adoption, and Dependent Care, Section on Developmental and Behavioral Pediatrics (2012) The Lifelong Effects of Early Childhood Adversity and Toxic Stress. Pediatrics 129: E232–E246.
16. Brown LA, Khousbouei H, Goodwin JS, Irvin-Wilson CV, Ramesh A, et al. (2007) Down-regulation of early ionotrophic glutamate receptor subunit developmental expression as a mechanism for observed plasticity deficits following gestational exposure to benzo(a)pyrene. Neurotoxicology 28: 965–978.
17. Wormley DD, Ramesh A, Hood DB (2004) Environmental contaminant-mixture effects on CNS development, plasticity, and behavior. Toxicol Appl Pharmacol 197: 49–65.
18. Grova N, Valley A, Turner JD, Morel A, Muller CP, et al. (2007) Modulation of behavior and NMDA-R1 gene mRNA expression in adult female mice after sub-acute administration of benzo(a)pyrene. Neurotoxicology 28: 630–636.
19. Schellenberger MT, Grova N, Farinelle S, Willième S, Schroeder H, et al. (2013) Modulation of benzo[a]pyrene induced neurotoxicity in female mice actively immunized with a B[a]P–diphtheria toxoid conjugate. Toxicology and Applied Pharmacology 271: 175–183.
20. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, et al. (2006) Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect 114: 1287–1292.
21. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, et al. (2009) Prenatal polycyclic aromatic hydrocarbon exposure and child intelligence at age 5. Pediatrics 124: e195–e202.
22. Bostic JQ, Prince JB (2008) Child and adolescent psychiatric disorders. In: Stern TA, Rosenbaum JF, Fava M, Biederman J, Rauch SL, editors.Massachusetts General Hospital Comprehensive Clinical Psychiatry. 1st ed. Philadelphia, PA: Elsevier Mosby.
23. Wilens TE, Biederman J, Brown S, Tanguay S, Monuteaux MC, et al. (2002) Psychiatric Comorbidity and Functioning in Clinically Referred Preschool Children and School-Age Youths With ADHD. Journal of the American Academy of Child & Adolescent Psychiatry 41: 262–268.
24. Spencer TJ, Biederman J, Mick E (2007) Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. J Pediatr Psychol 32: 631–642.
25. Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, et al. (1992) Further Evidence for Family-Genetic Risk-Factors in Attention-Deficit Hyperactivity Disorder - Patterns of Comorbidity in Probands and Relatives in Psychiatrically and Pediatrically Referred Samples. Archives of General Psychiatry 49: 728–738.
26. Spencer T, Biederman J, Wilens T (1999) Attention-deficit/hyperactivity disorder and comorbidity.Pediatr Clin North Am 46: 915–927, vii.
27. Charach A, Yeung E, Climans T, Lillie E (2011) Childhood Attention-Deficit/Hyperactivity Disorder and Future Substance Use Disorders: Comparative

Meta-Analyses. Journal of the American Academy of Child and Adolescent Psychiatry 50: 9–21.
28. Lee SS, Humphreys KL, Flory K, Liu R, Glass K (2011) Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev 31: 328–341.
29. Groenman AP, Oosterlaan J, Rommelse N, Franke B, Roeyers H, et al. (2013) Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. Addiction 108: 1503–1511.
30. Shaw M, Hodgkins P, Caci H, Young S, Kahle J, et al. (2012) A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. BMC Med 10: 99.
31. Banerjee TD, Middleton F, Faraone SV (2007) Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr 96: 1269–1274.
32. Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, et al. (2011) Update on environmental risk factors for attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 13: 333–344.
33. Siddique S, Banerjee M, Ray MR, Lahiri T (2011) Attention-deficit hyperactivity disorder in children chronically exposed to high level of vehicular pollution. Eur J Pediatr 170: 923–929.
34. Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, et al. (2013) Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. Environ Health Perspect 121: 731–736.
35. Chiu YHM, Bellinger DC, Coull BA, Anderson S, Barber R, et al. (2013) Associations between Traffic-Related Black Carbon Exposure and Attention in a Prospective Birth Cohort of Urban Children. Environ Health Perspect 121: 859–864.
36. Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, et al. (2003) Effects of transplacental exposure to environmental pollutants on birth outcomes in a multi-ethnic population. Environ Health Perspect 111: 201–205.
37. Schuurmans C, Kurrasch DM (2013) Neurodevelopmental consequences of maternal distress: what do we really know? Clinical Genetics 83: 108–117.
38. Bergman K, Sarkar P, O'Connor TG, Modi N, Glover V (2007) Maternal Stress During Pregnancy Predicts Cognitive Ability and Fearfulness in Infancy. Journal of the American Academy of Child & Adolescent Psychiatry 46: 1454–1463.
39. Barry TD, Dunlap ST, Cotten SJ, Lochman JE, Wells KC (2005) The Influence of Maternal Stress and Distress on Disruptive Behavior Problems in Boys. Journal of the American Academy of Child & Adolescent Psychiatry 44: 265–273.
40. Dohrenwend BS, Krasnoff L, Askenacy A, Dohrenwend B (1978) Exemplification of a method for scaling life events: the PERI life events scale. J Health Soc Behavior 19: 205–229.
41. Brown L, Sherbenou RJ, Johnson SK (1990) Test of non-verbal intelligence: a language-free measure of cognitive ability. 2nd edition. Austin, Tx: PRO-ED, Inc.
42. Caldwell BM, Bradley RH (1979) Home observation for measurement of the environment. Little Rock, AK: University of Arkansas Press.
43. Conners C, Erhardt D, Sparrow E (1999) Conners' Adult ADHD rating scales: Technical manual. New York: Multi-Health Systems.
44. Todd RD, Rasmussen ER, Neuman RJ, Reich W, Hudziak JJ, et al. (2001) Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. Am J Psychiatry 158: 1891–1898.
45. Achenbach T, Rescorla L (2001) Child Behavior Checklist for age 6–18. Burlington VT: ASEBA, 6-1-01 Edition.
46. Alexandrov K, Rojas M, Geneste O, Castegnaro M, Camus AM, et al. (1992) An improved fluorometric assay for dosimetry of benzo(a)pyrene diol-epoxide-DNA adducts in smokers' lung: comparisons with total bulky adducts and aryl hydrocarbon hydroxylase activity. Cancer Res 52: 6248–6253.
47. Li Z, Romanoff LC, Trinidad DA, Hussain N, Jones RS, et al. (2006) Measurement of urinary monohydroxy polycyclic aromatic hydrocarbons using automated liquid-liquid extraction and gas chromatography/isotope dilution high-resolution mass spectrometry. Anal Chem 78: 5744–5751.
48. Li Z, Sandau CD, Romanoff LC, Caudill SP, Sjodin A, et al. (2008) Concentration and profile of 22 urinary polycyclic aromatic hydrocarbon metabolites in the US population. Environ Res 107: 320–331.
49. Miller RL, Garfinkel R, Lendor C, Hoepner L, Li Z, et al. (2010) Polycyclic aromatic hydrocarbon metabolite levels and pediatric allergy and asthma in an inner-city cohort. Pediatr Allergy Immunol 21: 260–267.
50. Jongeneelen FJ, van Leeuwen FE, Oosterink S, Anzion RB, van der Loop F, et al. (1990) Ambient and biological monitoring of cokeoven workers: determinants of the internal dose of polycyclic aromatic hydrocarbons. Br J Ind Med 47: 454–461.
51. Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM (2004) Temporal variability of urinary phthalate metabolite levels in men of reproductive age. Environ Health Perspect 112: 1734–1740.
52. Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, et al. (2012) Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environ Health Perspect 120: 1190–1194.
53. Achenbach T, Rescorla L (2001) Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families.
54. Conners CK (1997) Conners' Rating Scales- Revised (CRS-R): User's Manual Toronto, ON: Multi-Health Systems Inc.
55. Conners CK, Parker JDA, Sitarenios G, Epstein JN (1998) The Revised Conners' Parent rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. Journal of Abnormal Child Psychology 26: 2567–2268.
56. Rodriguez-Barranco M, Lacasana M, Aguilar-Garduno C, Alguacil J, Gil F, et al. (2013) Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Sci Total Environ 454–455: 562–577.
57. Cornelius MD, De Genna NM, Leech SL, Willford JA, Goldschmidt L, et al. (2011) Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of adolescent mothers. Neurotoxicol Teratol 33: 137–144.
58. Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D (2007) Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ Health Perspect 115: 122–127.
59. Wasserman GA, Staghezza-Jaramillo B, Shrout P, Popovac D, Graziano J (1998) The effect of lead exposure on behavior problems in preschool children. Am J Public Health 88: 481–486.
60. American Psychiatric Association, American Psychiatric Association, Task Force on DSM-IV (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association. xxxvii, 943 p. p.
61. de Graaf R, Kessler RC, Fayyad J, ten Have M, Alonso J, et al. (2008) The prevalence and effects of adult attention-deficit/hyperactivity disorder (ADHD) on the performance of workers: results from the WHO World Mental Health Survey Initiative. Occup Environ Med 65: 835–842.
62. Kupper T, Haavik J, Drexler H, Ramos-Quiroga JA, Wermelskirchen D, et al. (2012) The negative impact of attention-deficit/hyperactivity disorder on occupational health in adults and adolescents. Int Arch Occup Environ Health 85: 837–847.
63. Wu SY, Gau SS (2013) Correlates for academic performance and school functioning among youths with and without persistent attention-deficit/hyperactivity disorder. Res Dev Disabil 34: 505–515.
64. Jacobson LA, Ryan M, Denckla MB, Mostofsky SH, Mahone EM (2013) Performance Lapses in Children with Attention-Deficit/Hyperactivity Disorder Contribute to Poor Reading Fluency. Arch Clin Neuropsychol.
65. Ek U, Westerlund J, Holmberg K, Fernell E (2011) Academic performance of adolescents with ADHD and other behavioural and learning problems -a population-based longitudinal study. Acta Paediatr 100: 402–406.
66. Strine TW, Lesesne CA, Okoro CA, McGuire LC, Chapman DP, et al. (2006) Emotional and behavioral difficulties and impairments in everyday functioning among children with a history of attention-deficit/hyperactivity disorder. Prev Chronic Dis 3: A52.
67. CDC (2013) ADHD, Data and Statistics, National Center on Birth Defects and Developmental Disabilities.
68. Pelham WE, Foster EM, Robb JA (2007) The economic impact of attention-deficit/hyperactivity disorder in children and adolescents. J Pediatr Psychol 32: 711–727.
69. Perera FP, Tang D, Whyatt R, Lederman SA, Jedrychowski W (2005) DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center Area, Poland, and China. Cancer Epidemiol Biomarkers Prev 14: 709–714.
70. Castano-Vinyals G, D'Errico A, Malats N, Kogevinas M (2004) Biomarkers of exposure to polycyclic aromatic hydrocarbons from environmental air pollution. Occup Environ Med 61: e12.
71. Strickland P, Kang D, Sithisarankul P (1996) Polycyclic aromatic hydrocarbon metabolites in urine as biomarkers of exposure and effect. Environ Health Perspect 104 Suppl 5: 927–932.
72. Zhao ZH, Quan WY, Tian DH (1990) Urinary 1-Hydroxypyrene as an Indicator of Human Exposure to Ambient Polycyclic Aromatic-Hydrocarbons in a Coal-Burning Environment. Science of the Total Environment 92: 145–154.
73. Archibong AE, Inyang F, Ramesh A, Greenwood M, Nayyar T, et al. (2002) Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. Reprod Toxicol 16: 801–808.
74. Bui QQ, Tran MB, West WL (1986) A comparative study of the reproductive effects of methadone and benzo(a)pyrene in the pregnant and pseudopregnant rat. Toxicology 42: 195–204.
75. Takeda K, Tsukue N, Yoshida S (2004) Endocrine-disrupting activity of chemicals in diesel exhaust and diesel exhaust particles. Environ Sci 11: 33–45.
76. Dejmek J, Solansky I, Benes I, Lenicek J, Sram RJ (2000) The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environ Health Perspect 108: 1159–1164.
77. Manchester DK, Gordon SK, Golas CL, Roberts EA, Okey AB (1987) Ah receptor in human placenta: stabilization by molybdate and characterization of binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin, 3-methylcholanthrene, and benzo(a)pyrene. Cancer Res 47: 4861–4868.
78. Meyn MS (1995) Ataxia-telangiectasia and cellular responses to DNA damage. Cancer Res 55: 5991–6001.
79. Nicol CJ, Harrison ML, Laposa RR, Gimelshtein IL, Wells PG (1995) A teratologic suppressor role for p53 in benzo[a]pyrene-treated transgenic p53-deficient mice. Nat Genet 10: 181–187.
80. Wood KA, Youle RJ (1995) The role of free radicals and p53 in neuron apoptosis in vivo. J Neuroscience 15: 5851–5857.

81. Saunders CR, Das SK, Ramesh A, Shockley DC, Mukherjee S (2006) Benzo(a)pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. J Appl Toxicol 26: 427–438.
82. Wilson VL, Jones PA (1983) Inhibition of DNA methylation by chemical carcinogens in vitro. Cell 32: 239–246.
83. Stiles J, Jernigan TL (2010) The basics of brain development. Neuropsychol Rev 20: 327–348.
84. Garzon DL, Huang H, Todd RD (2008) Do Attention Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder Influence Preschool Unintentional Injury Risk? Archives of Psychiatric Nursing 22: 288–296.
85. Wood JJ (2006) Effect of anxiety reduction on children's school performance and social adjustment. Dev Psychol 42: 345–349.
86. Knapp M, King D, Healey A, Thomass C (2011) Economic Outcomes in Adulthood and their Associations with Antisocial Conduct, Attention Deficit and Anxiety Problems in Childhood. Journal of Mental Health Policy and Economics 14: 137–147.
87. Kotsopoulos N, Connolly MP, Sobanski E, Postma MJ (2013) The fiscal consequences of ADHD in Germany: a quantitative analysis based on differences in educational attainment and lifetime earnings. J Ment Health Policy Econ 16: 27–33.

PLOS ONE

RESEARCH ARTICLE

Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years

Pam Factor-Litvak[1]*, Beverly Insel[1], Antonia M. Calafat[2], Xinhua Liu[3], Frederica Perera[4], Virginia A. Rauh[5], Robin M. Whyatt[4]

1. Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **2.** National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **3.** Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **4.** Department of Environmental Health Sciences, Columbia Center for Children's Environmental Health, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **5.** Heilbrunn Department of Population and Family Health, Mailman School of Public Health, Columbia University, New York, New York, United States of America

*prf1@columbia.edu

Citation: Factor-Litvak P, Insel B, Calafat AM, Liu X, Perera F, et al. (2014) Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years. PLoS ONE 9(12): e114003. doi:10.1371/journal.pone.0114003

Editor: David O. Carpenter, Institute for Health & the Environment, United States of America

Received: July 29, 2014

Accepted: October 29, 2014

Published: December 10, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. Ethical restrictions make data unsuitable for public deposition. An anonymized data set can be requested from the corresponding author.

Funding: National Institute of Environmental Health Sciences (NIEHS) grants R01ES013543, R01ES014393, and R01ES08977 and by NIEHS/United States Environmental Protection Agency grant P50 ES09600/RD 83214101. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background: Prior research reports inverse associations between maternal prenatal urinary phthalate metabolite concentrations and mental and motor development in preschoolers. No study evaluated whether these associations persist into school age.

Methods: In a follow up of 328 inner-city mothers and their children, we measured prenatal urinary metabolites of di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBzP), di-isobutyl phthalate (DiBP), di-2-ethylhexyl phthalate and diethyl phthalate in late pregnancy. The Wechsler Intelligence Scale for Children, 4th edition was administered at child age 7 years and evaluates four areas of cognitive function associated with overall intelligence quotient (IQ).

Results: Child full-scale IQ was inversely associated with prenatal urinary metabolite concentrations of DnBP and DiBP: b = −2.69 (95% confidence interval [CI] = −4.33, −1.05) and b = −2.69 (95% CI = −4.22, −1.16) per log unit increase. Among children of mothers with the highest versus lowest quartile DnBP and DiBP metabolite concentrations, IQ was 6.7 (95% CI = 1.9, 11.4) and 7.6 (95% CI = 3.2, 12.1) points lower, respectively. Associations were unchanged after control for cognition at age 3 years. Significant inverse associations were also seen between maternal prenatal metabolite concentrations of DnBP and DiBP and child processing speed, perceptual reasoning and working memory; DiBP and child verbal comprehension; and BBzP and child perceptual reasoning.

Conclusion: Maternal prenatal urinary metabolite concentrations measured in late pregnancy of DnBP and DiBP are associated with deficits in children's intellectual development at age 7 years. Because phthalate exposures are ubiquitous and concentrations seen here within the range previously observed among general populations, results are of public health significance.

Introduction

Phthalates are a class of high production chemicals widely used as plasticizers and additives in consumer and personal care products [1]. Many phthalates are endocrine disruptors which may operate through multiple mechanisms including perturbations in thyroid hormone and testosterone levels [2, 3]. Exposures to phthalates are ubiquitous [4, 5]. Urinary concentrations of phthalate metabolites are used as internal dosimeters because urinary enzymatic activity is negligible [6]; thus metabolite concentrations in urine reflect an individual's internal exposure to phthalates, rather than phthalate contaminants introduced during sample collection and processing. Prior studies have shown moderate reproducibility (i.e. intraclass correlation coefficients ranging from approximately 0.20 to 0.77) for measurements of several phthalate metabolite concentrations in repeat spot urine samples [5, 7–9].

Limited epidemiologic studies have reported inverse associations between phthalate metabolites in maternal prenatal urine and child mental, motor and behavioral development [5, 10]. Previously, we reported that maternal prenatal urinary concentrations of mono-n-butyl phthalate (MnBP) and monoisobutyl phthalate (MiBP), the main metabolites of di-n-butyl phthalate (DnBP) and di-isobutyl phthalate (DiBP), respectively, were inversely associated with child age 3 year motor development and increased the risk of motor delay [5]. Among girls, MiBP was also inversely associated with mental development [5]. Experimental animal studies find inverse associations between prenatal exposure to di-2-ethylhexyl phthalate (DEHP) and DnBP and learning and memory in the offspring [11, 12]. No prior studies have evaluated associations between prenatal phthalate exposures on child intelligence quotient (IQ) in school-age children. However, a cross-sectional study of Korean 3rd and 4th grade children found inverse associations between DEHP metabolites in child urine and IQ [13]. Based on these findings, we hypothesized that prenatal phthalates exposures would be inversely associated with child IQ at age 7 years.

Methods

We studied 328 inner-city women and their 7-year old children from the Columbia Center for Children's Environmental Health (CCCEH) longitudinal birth cohort of 727 pregnant women who delivered between 1998 and 2006. The

original aim of the cohort was to examine the associations between exposure to air pollutants and pregnancy outcomes and child development. Enrollment, exclusion criteria, and a description of the cohort have been described previously [14]. Women 18–35 years old who self-identified as either African American or Dominican were enrolled through prenatal clinics associated with Harlem and New York Presbyterian Hospitals. Women were excluded if they reported active smoking, use of other tobacco products or illicit drugs, had diabetes, hypertension or known HIV, had their first prenatal visit after the 20th week of gestation or had resided in the study area for less than one year prior to pregnancy. Mother-child pairs were selected for participation in the current study if phthalate metabolite concentrations had been measured in spot urine samples collected during pregnancy and if the child had completed the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) at age 7 years. We excluded women with active smoking during pregnancy verified by maternal and/or umbilical cord plasma cotinine >15 ng/ml at delivery (n=30), no or insufficient urine for measurement of phthalate metabolites (n=286), and those lost to follow-up prior to child age 7 years (n=83). Among women who had prenatal phthalate measurements, the retention rate was 80% at the 7-year follow-up. The 328 study subjects did not differ significantly from the remaining subjects in the CCCEH cohort in terms of demographics (race/ethnicity, maternal marital status, education level, household income, proportion receiving Medicaid), prenatal alcohol consumption, child sex, gestational age, and birth weight (all p-values>0.05). Moreover, study children did not differ from the remaining children with respect to mental and motor development scores at age 3 years.

Ethics Statement

Institutional review boards at the Columbia University Medical Center and the Centers for Disease Control and Prevention (CDC) approved the study and all consent procedures for the study. Written informed consent was obtained from all participating mothers, who also provided written informed consent on behalf of their children, and written informed assent was obtained from all children starting at age 7 years.

Urine sample collection and phthalate measurements

Spot urine samples were collected during the 3rd trimester of pregnancy (average 34.0 ± 3.0 weeks, median 33.9) and from the children at ages 3 (n=241) and 5 (n=277) years. Samples were analyzed for metabolites of 5 phthalates (DnBP, BBzP, DiBP, DEHP and diethylphthalate) at the CDC as described [15]. Specific gravity was measured in the urine samples using a handheld refractometer and used to control for urinary dilution (Atago PAL 10-S, Bellevue, WA) [7].

As a measure of reliability, we calculated intraclass correlation coefficients (ICCs) for the phthalate metabolites in serial spot urine samples collected biweekly from 48 women in the CCCEH cohort over 6–8 weeks late in pregnancy

(n=135 samples, 2–4 repeats per woman). Adjusting for specific gravity, ICCs were 0.77 for MBzP, 0.65 for mono-*n*-butyl phthalate (MnBP), and 0.60 for monoisobutyl phthalate (MiBP) and ranged from 0.27 to 0.42 for the DEHP metabolites [5].

Measures of child mental development

The Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) [16] was administered to children at age 7 years. The instrument measures four areas of mental functioning that are associated with, but distinct from, overall IQ. The Verbal Comprehension Index is a measure of verbal concept formation; the Perceptual Reasoning Index measures nonverbal and fluid reasoning; the Working Memory Index assesses children's ability to memorize new information, hold it in short-term memory, concentrate, and manipulate information; and the Processing Speed Index assesses ability to focus attention and quickly scan, discriminate, and sequentially order visual information. Full-Scale IQ score combines the four composite indices. All WISC-IV scales are standardized to a mean of 100 and standard deviation (SD) of 15. The WISC-IV has been shown in prior research to be sensitive to effects of low-dose neurotoxicant exposures on cognition [17–19].

Model covariates

Information on potential confounders was gathered by questionnaires administered to the mother during pregnancy and at various postnatal intervals by trained bi-lingual interviewers and by review of maternal and infant medical records. Variables of interest included race/ethnicity, maternal education and marital status, household income, parity, gestational age, birth weight, child sex, breastfeeding history, exposure to tobacco smoke in the home, prenatal alcohol consumption, and prenatal psychosocial factors including maternal self-report of hardship during pregnancy (i.e., lack of food, clothing, housing, gas or electricity, or medicines) and satisfaction with overall living conditions. Maternal demoralization was measured by the 27-item Psychiatric Epidemiology Research Instrument-Demoralization Scale [20]. Maternal intelligence was assessed by the Test of Non-Verbal Intelligence, third edition [21], a language-free measure of general intelligence, which is relatively stable and free of cultural bias. The quality of the care-taking environment was measured by the Home Observation for Measurement of the Environment (HOME) scale [22] at child age 38.4 $\pm$ 6.2 months.

Statistical analysis

Linear regression models were used to examine relationships between prenatal exposures to the five phthalates (assessed from the urinary metabolite concentrations) and WISC-IV outcomes. Phthalate metabolite concentrations below the limit of detection (LOD) (one for monobenzyl phthalate (MBzP), one

for mono-isobutyl phthalate (MiBP) and 53 for mono-2-ethylhexyl phthalate (MEHP)) were assigned a value of LOD/$\sqrt{2}$ [23]. The distributions of the phthalate metabolite concentrations were right skewed and transformed using the natural logarithm to improve model fitting and reduce the influence of extreme values. In our analyses, each metabolite was considered as a continuous variable and was categorized into quartiles to explore the shape of the dose response relationship. The final regression models included covariates that were *a priori* potential confounders based on previous literature and a directed acyclic graph, and that were associated with at least one WISC-IV subscale or the total WISC-IV score [5, 17, 18]. Missing values for covariates were imputed as follows: *a*) twelve missing values for maternal IQ were imputed by a linear regression model with race/ethnicity, maternal education and age as predictors (model $R^2=0.13$); *b*) twenty missing observations for the HOME scale were imputed by linear regression model with race/ethnicity, maternal education and IQ, and household income as predictors (model $R^2=0.18$); *c*) ten missing observations for prenatal maternal alcohol consumption were given a category of missing. Sensitivity analyses were conducted for observations with no missing data (reducing the sample size to 290); results were essentially unchanged from those reported here. We used maternal urinary concentrations of mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) as the proxy for exposure to DEHP. All DEHP metabolites were highly correlated with each other (Spearman correlation coefficient $r \geq 0.8$) [25]. In a sensitivity analysis results using MEHP as the DEHP exposure proxy were essentially the same. Analyses were repeated using the molar sum of all four DEHP metabolites, also with essentially the same results. Urinary specific gravity was included in all models to control for dilution [7]. We evaluated confounding in two ways. First, we constructed a directed acyclic graph to determine potential confounders. Second, for each potential confounder, we assessed the change in the estimated regression coefficient between the exposure of interest (i.e. specific phthalate metabolite) and outcome (i.e. either the WISC IQ measure or the WISC subscale measure) with and without the potential confounder. We included variables in the model if their inclusion changed the estimated regression coefficient between exposure and outcome by more than.5 standard deviation units. To evaluate whether sex of the child was an effect modifier, we conducted analyses separately by sex, and assessed whether the estimated coefficients differed using the Wald test. In secondary analyses, we included a measure of cognitive performance at age 3 years (the Mental Development Index (MDI) from the Bayley Scales of Infant Development-second edition (1993). Additionally, we evaluated whether child age 3 and 5 years urinary phthalate metabolite concentrations were associated with WISC-IV outcomes at age 7 years. We also evaluated whether other contaminants, namely lead, chlorpyrifos, and polycyclic aromatic hydrocarbons (PAHs), were potential confounders. With the exception of a negative correlation between PAHs and one phthalate metabolite (MiBP) ($r=-0.13$, $p=.02$), no correlations were found between any other contaminant and phthalate metabolite. In a sensitivity analysis, we included PAHs in the regression model relating MiBP to the cognitive outcomes; the magnitudes of the

regression coefficients became stronger and more statistically significant. Analyses were conducted using SAS (version 9.3 SAS Institute Inc., Cary, NC).

Results

Maternal sociodemographic characteristics, infant birth and child characteristics and distributions of model covariates and outcome variables are presented in Table 1. Eighteen children (5.5%) were administered the test in Spanish. Table 2 shows the distribution of the urinary phthalate metabolite concentrations in maternal prenatal spot samples. Metabolites were detected in 99.7–100% of the samples, except for MEHP in which 16% of the measures were below the LOD. Nevertheless, for the 53 measures that were below the LOD, using the actual concentrations or the assignment of a value $(1/\sqrt{2}) \times \text{LOD}$ produced essentially the same results. Spearman correlation coefficients between the specific gravity adjusted maternal prenatal metabolite concentrations ranged from 0.15 (for monoethyl phthalate (MEP) and both MBzP and MEHHP) to 0.63 (for MiBP and MnBP). Correlations for the urinary phthalate metabolite concentrations in child age 3 and 5 year samples were similar (data not shown). However, correlations between each phthalate metabolite across ages (prenatal, age 3 and 5 years) were not statistically significant. The correlation between Bayley MDI score and full scale IQ at age 7 was 0.43 ($p<.0001$) and between maternal IQ and full scale IQ at age 7 was 0.26 ($p<.0001$).

In the total cohort (table 3), full scale IQ was inversely associated with $\log_e$MnBP (b=–2.69 [95% CI=–4.33, –1.05]) and $\log_e$MiBP (b=–2.69 [95% CI=–4.22, –1.16]) but not with the other phthalate metabolites. Additonally, $\log_e$MnBP, $\log_e$MiBP and $\log_e$MBzP were significantly inversely associated with perceptual reasoning, $\log_e$MnBP and $\log_e$MiBP with processing speed, $\log_e$MiBP with verbal comprehension, and $\log_e$MnBP and $\log_e$MiBP with working memory. There were no significant associations between maternal MEHP, MEHHP or MEP concentrations and any of the WISC-IV scales. There were some differences in the estimated regression coefficients relating the exposures to outcomes between boys and girls, although with one exception none reached statistical significance. Specifically, associations between MnBP and full scale IQ and perceptual reasoning appeared stronger among girls than boys, and associations between MnBP and processing speed appeared stronger among boys. Additionally, associations between MBzP and perceptual reasoning and between MiBP and verbal comprehension appeared stronger among boys. MnBP was associated with working memory and the size of the associations was significantly larger among girls than boys ($p=0.02$ Wald test). Controlling for postnatal year three and year five phthalate metabolites concentrations did not alter the association between prenatal phthalate exposures and the WISC outcomes at age 7 years.

Full scale IQ scores among children born to mothers with urinary MnBP and MiBP concentrations in the highest compared to the lowest quartiles were 6.6, 95% CI=(1.89, 11.41) and 7.6, 95% CI=(3.2, 12.1) points lower, respectively

Table 1. Subject demographics, distribution of model covariates, and outcome variables (N=328).

Characteristic	Value (%)
Maternal age at prenatal interview (yr)	25.3±4.8
Ethnicity	
African American	215 (34.5)
Dominican or other Hispanic	113 (65.5)
Maternal education	
<High school degree	119 (36.3)
≥High school diploma or general educational development (GED)	209 (63.7)
Marital status	
Never married	220 (67.1)
Ever Married[a]	108 (32.9)
Maternal IQ (n=316)	84.6±13.3
HOME scale (n=308)	39.2±6.3
Prenatal alcohol consumption (N=318)	82 (25.8)
Child sex	
Male	155 (47.3)
Female	173 (52.7)
Child age at WISC-IV (yr)	7.05±0.20
WISC-IV Outcome variables	
Full Scale Composite Score	97.1±13.1
Perceptual Reasoning Composite Score	99.3±14.0
Processing Speed Composite Score	98.9±14.6
Verbal Comprehension Composite Score	94.4±12.7
Working Memory Composite Score	98.5±14.9

Values are mean ± SD or n (percent). Unless indicated, N=328.
[a]Includes living with same partner for >7 years.

doi:10.1371/journal.pone.0114003.t001

(Figure 1). Similar differences were found for the perceptual reasoning, processing speed and working memory scores. Children whose mother had the highest versus lowest concentration of MBzP and MiBP had significantly lower scores on

Table 2. Distribution of Phthalate metabolites (ng/ml) in maternal spot urine during the third trimester of pregnancy (n=328).

Metabolite	Mean	95% CI	LOD*	%<LOD	Range	25%	Median	75%
MnBP	37.6	(33.5, 42.3)	0.6	0	1.2–1,110	19.4	38.0	79.8
MBzP	13.4	(11.6, 15.4)	0.22	0.3	ND–550.4	5.8	14.4	30.0
MEHHP	22.3	(19.4, 25.5)	0.7	0	1.1–1750	10.6	21.8	47.2
MEHP	4.95	(4.2, 5.7)	1.2	16.2	ND–613	1.9	4.9	12.4
MEP	160.5	(140.4, 183.4)	0.53	0	7.8–6045.6	69.9	141.5	334.1
MiBP	9.1	(8.1. 10.2)	0.3	0.3	ND–374.4	5.0	9.2	19.0

ND=not detected.

doi:10.1371/journal.pone.0114003.t002

Table 3. Estimated adjusted regression coefficients relating maternal prenatal urinary phthalate concentrations to the WISC-IV full scale IQ and subscales at child age 7 years.

	B-Coefficient (95% CI)						Child sex
	Total		Girls		Boys		Difference
Metabolite (log base e)	(n=328)		(n=173)		(n=155)		*p*-value[@]
Full Scale							
MBnP	−2.69	(−4.33,−1.05)**	−3.15	(−5.44,−0.87)**	−1.89	(−4.34, 0.56)	0.46
MBzP	−1.18	(−2.40, 0.05)	−0.84	(−2.52, 0.83)	−1.48	(−3.35, 0.38)	0.61
MEHHP	0.16	(−1.16, 1.48)	0.34	(−1.35, 2.03)	0.26	(−1.87, 2.40)	0.96
MEHP	−0.30	(−1.42, 0.82)	−0.05	(−1.53, 1.42)	0.09	(−1.92, 2.11)	0.74
MEP	−0.17	(−1.46, 1.13)	−0.75	(−2.53, 1.03)	0.40	(−1.53, 2.33)	0.39
MiBP	−2.69	(−4.22,−1.16)**	−2.38	(−4.50,−0.26)*	−2.92	(−5.17,−0.67)*	0.73
Perceptual Reasoning							
MnBP	−2.58	(−4.40,−0.76)**	−3.55	(−5.96,−1.14)**	−1.50	(−4.36, 1.35)	0.28
MBzP	−1.65	(−3.00,−0.30)*	−1.13	(−2.89, 0.64)	−2.45	(−4.60,−0.31)*	0.35
MEHHP	0.18	(−1.28, 1.64)	0.03	(−1.76, 1.82)	0.56	(−1.92, 3.04)	0.73
MEHP	−0.07	(−1.30, 1.17)	−0.09	(−1.65, 1.48)	0.01	(−2.00, 2.03)	0.94
MEP	−0.62	(−2.05, 0.81)	−0.67	(−2.56, 1.22)	−0.57	(−2.81, 1.67)	0.95
MiBP	−2.41	(−4.11,−0.71)*	−2.39	(−4.64,−0.14)*	−2.41	(−5.05, 0.23)	0.99
Processing Speed							
MnBP	−2.01	(−3.91,−0.11)*	−1.29	(−4.04, 1.45)	−2.85	(−5.63,−0.08)*	0.43
MBzP	−0.47	(−1.88, 0.95)	−0.74	(−2.72, 1.23)	−0.02	(−2.17, 2.12)	0.63
MEHHP	−0.41	(−1.91, 1.10)	−0.84	(−2.83, 1.15)	0.25	(−2.19, 2.68)	0.50
MEHP	−0.95	(−2.23, 0.33)	−0.93	(−2.67, 0.80)	−0.94	(−2.92, 1.03)	0.99
MEP	0.54	(−0.95, 2.03)	−0.26	(−2.37, 1.84)	1.21	(−0.99, 3.41)	0.34
MiBP	−1.94	(−3.72,−0.17)*	−1.94	(−4.46, 0.58)	−2.10	(−4.70, 0.50)	0.93
Verbal Comprehensionn oCnsion							
MnBP	−1.52	(−3.06, 0.02)	−1.06	(−3.29, 1.16)	−1.64	(−3.90, 0.62)	0.72
MBzP	−0.78	(−1.92, 0.36)	−0.46	(−2.06, 1.14)	−1.07	(−2.79, 0.66)	0.61
MEHHP	0.46	(−0.76, 1.69)	0.86	(−0.75, 2.47)	0.09	(−1.88, 2.06)	0.55
MEHP	−0.28	(−1.32, 0.76)	−0.01	(−1.42, 1.40)	−0.60	(−2.20, 1.00)	0.58
MEP	0.10	(−1.30, 1.11)	−0.71	(−2.42, 0.99)	0.52	(−1.26, 2.31)	0.32
MiBP	−2.08	(−3.51,−0.65)**	−1.05	(−3.10, 1.00)	−3.04	(−5.11,−0.98)**	0.18
Working Memory							
MnBP	−2.57	(−4.55,−0.59)**	−4.73	(−7.53,−1.93)**	−0.07	(−2.92, 2.78)	0.02
MBzP	−0.68	(−2.16, 0.80)	−0.59	(−2.67, 1.48)	−0.50	(−2.68, 1.67)	0.95
MEHHP	0.36	(−1.23, 1.94)	1.16	(−0.92, 3.25)	−0.29	(−2.76, 2.18)	0.37
MEHP	0.55	(−0.79, 1.89)	1.22	(−0.60, 3.04)	0.09	(−1.92, 2.11)	0.41
MEP	−0.39	(−1.95, 1.17)	−1.06	(−3.26, 1.15)	0.28	(−1.96, 2.52)	0.40
MiBP	−1.98	(−3.84,−0.12)*	−2.53	(−5.16, 0.11)	−1.27	(−3.92, 1.38)	0.51

*$p<0.05$, **$p\leq0.01$. [@]Wald Test.
Adjusted model for specific gravity, maternal IQ, ethnicity, alcohol use during pregnancy, education, marital status, total home score, and sex of child.

doi:10.1371/journal.pone.0114003.t003

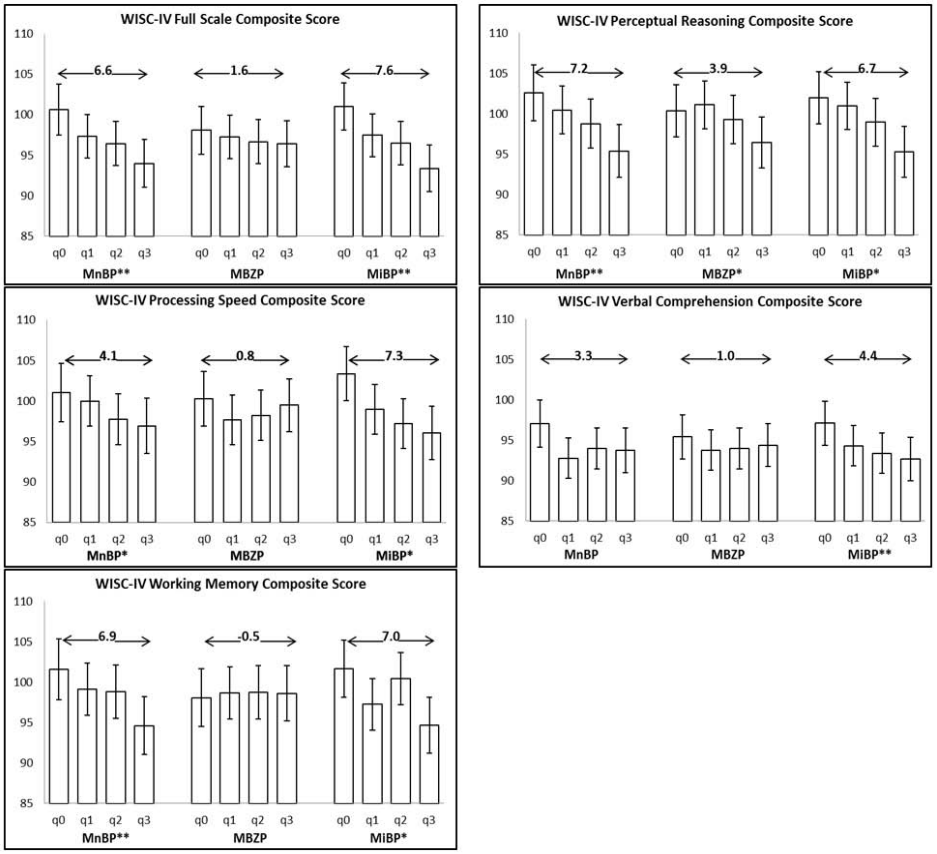


Figure 1. Adjusted mean WISC-IV total score and subtest scored by lowest to highest quartile of maternal prenatal phthalate metabolite concentration (where q0=lowest quartile, q4=highest quartile, q2 and q3 intermediate quartiles). Means adjusted for urine specific gravity, maternal IQ, ethnicity, alcohol use during pregnancy, education, marital status, quality of the home environment (HOME score) and sex of child. *$p<0.05$, **$p\leq0.01$.

doi:10.1371/journal.pone.0114003.g001

perceptual reasoning (by 3.9 points) and verbal comprehension (by 4.4 points), respectively.

Examination of postnatal phthalate exposure controlling for prenatal exposure suggested specific associations between MBzP measured at age 3 and several of the outcomes. Specifically, we found inverse associations between, $\log_e$ MBzP concentrations measured at age 3 were inversely associated with full-scale IQ (b=–1.52; 95% CI=(–2.71, –0.32)), perceptual reasoning (b=–1.68; 95% CI=(–3.01, –0.36)), and working memory (b=–2.2.47; 95% CI=(–3.92, –1.01)) at age 7 years (see Table S1). We observed no associations between concentrations of phthalate metabolites measured at age 5 years and IQ measured at age 7 years; nor did we see any significant associations between the WISC-IV scales and MnBP and MiBP measured at age 3 years. Finally, there was no change in the associations between prenatal urinary phthalate metabolites and any of the WISC outcomes after inclusion of the child age 3 years mental development index (MDI) on the

Bayley Scales of Infant Development. Associations also did not change when language of test administration was controlled.

Discussion

In our follow up study of children prenatally exposed to phthalates, we found significant associations between exposure to DnBP and DiBP and IQ measured at age 7 years, after adjusting for potential confounders. Compared to children born to women in the lowest 25th concentration percentile, children born to women above the 75th concentration percentile for MnBP and MiBP scored 6.6 and 7.6 points lower on 7 year IQ. Similar associations were found between these metabolites and perceptual reasoning, working memory and processing speed subscales of the WISC-IV. Differences in the estimates of association were found in boys and girls. Associations between maternal prenatal MnBP concentrations and child age 7 full scale IQ, perceptual reasoning and working memory were stronger among girls and associations between maternal prenatal MnBP and MiBP concentrations and processing speed and verbal comprehension, respectively, were stronger among boys. We note however, that with one exception the interactions between phthalate metabolites and sex did not reach conventional statistical significance criterions.

These findings extend our earlier observation of associations between prenatal exposure to phthalates and children's cognitive function and behavior at age 3 years[5]. In the earlier analysis, we found inverse associations between urinary concentrations of MnBP and MiBP and scores on the psychomotor development index (PDI) of the Bayley Scales of Infant Development (BSID) for both boys and girls, and an inverse association between MnBP concentrations and the mental development index (MDI) of the BSID in girls only. Taken together, our findings suggest adverse associations between prenatal phthalate exposure and cognition that persist into the early school years, with potentially meaningful implications for academic performance. We also find associations between MBzP measured at age 3 and full scale IQ, and the perceptual motor and working memory subscales at age 7, suggesting a role of postnatal exposure for specific phthalates.

Several studies have reported associations between prenatal phthalate exposure and neurodevelopment, but the literature is inconsistent regarding the specific phthalate metabolites examined and the finding of sex-specific associations. Engel, et al (2009) [24] found associations in girls, but not boys, between metabolites of high molecular weight phthalates (e.g. DEHP, BBzP) on the Brazelton Neonatal Behavioral Scale administered within five days of delivery. Yolton, et al (2011) [25] reported associations between the urinary concentrations of DEHP metabolites and suboptimal neurological reflexes in boys at 5 weeks of age. Kim, et al (2011) [10] found associations between urinary concentrations of DEHP metabolites and delays in both BSID mental and motor development and urinary concentrations of DnBP metabolite and delays in mental development in 6-month old Korean boys. These three studies are limited by the measure of

neurobehavioral assessment, which becomes more reliable as the children age. Tellez-Rojo et al (2013) [26] evaluated prenatal phthalate exposure and repeated BSID scores at ages 2, 2.5 and 3 years in 135 children enrolled in the ELEMENT study in Mexico and found associations with DEHP metabolites in sex-specific analyses only. A final, albeit cross sectional, study found inverse associations between metabolites of DEHP and DnBP and vocabulary development at ages 8–11 years among Korean children [13]. The inconsistent associations regarding the specific phthalates may be due to the variability in age of assessment (the BSID become more stable with increasing age at assessment), the WISC testing different constructs than the BSID, poor adjustment for the correlations between phthalate metabolites, and differences in the concentrations of phthalates in the specific populations. Nevertheless, the consistent pattern of associations between MnBP and MiBP across ages in our cohort lends support to our cognitive findings.

Comparison of the concentrations of phthalate metabolites in our study to those in the last reported NHANES data [27] find, as expected, slightly higher concentrations among women in our sample. However, the confidence intervals in our data and the NHANES data overlap substantially, suggesting that the concentrations in our study are still relevant.

There are several possible mechanisms underlying these associations. Phthalates may act as anti-androgens and lead to disruption in the normal sexual differentiation of the brain [28–30]; they may modulate the activity of aromatase in the developing brain and thus interfere with estrogen synthesis [31, 32]; they may interfere with thyroid hormone production [33–36, 29, 37–41]; and they may disrupt brain dopaminergic activity [42, 43] which is linked to inattention and hyperactivity [44]. These mechanisms may shed light on why the adverse associations are sex specific.

Our study has a number of strengths. First it is a prospective evaluation with assessment of exposure to phthalates not only in the prenatal period, but also at ages 3 and 5 years. It is noteworthy that our associations were primarily limited to prenatal concentrations of phthalate metabolites, with some additional associations seen for age 3 exposures, suggesting that there are critical periods of exposure related to adverse cognitive outcomes. Second, although our sample size was likely not sufficient to estimate sex-specific associations, we did observe several sex specific differences in associations. This is important given that many of the purported mechanisms for these associations are linked to brain concentrations of sex hormones. However, there are also some limitations. We are unable to identify specific times during pregnancy when phthalates could be related to outcomes as urine was only collected from the pregnant women in the third trimester. Because phthalates have a half- life of approximately 12 hours, single, spot urine measures do not reflect long term exposure. We evaluated reproducibility of these urine measures in a sample of 48 women who had repeat urine measures during the third trimester; the ICCs were 0.77 for MBzP, 0.65 for mono-*n*-butyl phthalate (MnBP), and 0.60 for monoisobutyl phthalate (MiBP) and ranged from 0.27 to 0.42 for the DEHP metabolites, indicating moderate reliability over a short time span. Strictly speaking, therefore, our results should be

specific to phthalate exposure during the third trimester. Restriction of the study sample to inner-city African American and Hispanics reduces the generalizability of the results, but likely also minimized residual confounding by socioeconomic status and race. We note that we also controlled for a variety of factor known to be associated with child IQ, namely maternal IQ, race/ethnic group, alcohol use during pregnancy, maternal education, marital status, other contaminants and HOME score. Birth weight, another predictor of child IQ, did not change the estimated associations between any phthalate metabolite and IQ. Further work in other ethnic and socioeconomic populations would be needed to generalize these results. We also measured a limited number of phthalate metabolites and thus cannot infer our results to other phthalates. We also could not evaluate the associations between phthalate exposure and school performance as these data are not available. Finally, there may be some measurement error in the categorization of phthalates exposure based on urinary metabolite concentrations because the correlations between measures of the same metabolite over relatively short intervals were moderate to low [9].

Given the observational nature of this study, we cannot conclude a causal relationship between late prenatal exposure to certain phthalates and reductions in IQ. Nevertheless, we have now observed consistent associations between exposure and outcomes measured at two time-points, one in the preschool years and one in the early school years, suggesting the results are not spurious and appear to be persistent. Indeed, the associations in the early school years are not diminished after control for MDI measured at age 3 years, suggesting a robust association. We note that the consistency of the associations over time has implications for public health and regulatory policy.

In conclusion, our analysis of the associations between prenatal phthalate exposure and IQ in the early school years showed significant decrements in IQ associated with two specific phthalates. These findings are important to inform policy makers of the potentially harmful effects of this class of chemicals.

Supporting Information

Table S1. Estimated coefficients of urinary phthalate concentrations in the linear model for WISC-IV when the children were 7 years of age. [a]Models include those with phthalate metabolite data at age 3. [b]Models include those with phthalate metabolite data at age 5. $^{*}p<0.05$, $^{**}p\leq 0.01$. The model controlled for specific gravity (prenatal, age 3, and age 5 as appropriate), maternal IQ, ethnicity, alcohol use during pregnancy, education, marital status, total home score, and sex of child.

doi:10.1371/journal.pone.0114003.s001 (DOCX)

Acknowledgments

The authors gratefully acknowledge the technical assistance of Manori Silva, Ella Samandar, Jim Preau, and Lily Jia in measuring the urinary concentrations of phthalate metabolites.

The findings expressed in this paper are the opinions of the authors and do not necessarily reflect the official opinion of the Centers for Disease Control and Prevention.

This work was supported by National Institute of Environmental Health Sciences (NIEHS) grants R01ES013543, R01ES014393, and R01ES08977 and by NIEHS/U.S. Environmental Protection Agency grant P50 ES09600/RD 83214101.

Author Contributions

Conceived and designed the experiments: PF-L VAR RMW. Performed the experiments: PF-L BI AMC XL FP VAR RMW. Analyzed the data: PF-L BI XL RMW. Contributed reagents/materials/analysis tools: AMC. Contributed to the writing of the manuscript: PF-L BI AMC XL FP VAR RMW.

References

1. **Sathyanarayana S** (2008) Phthalates and children's health. Curr Probl Pediatr Adolesc Health Care 38: 34–49.
2. **Braun JM, Sathyanarayana S, Hauser R** (2013) Phthalate exposure and children's health. Current opinion in pediatrics 25: 247–54.
3. **Bellinger DC** (2013). Prenatal Exposures to Environmental Chemicals and Children's Neurodevelopment: An Update. Saf Health Work 4: 1–11.
4. **CDC.** Fourth National Report on Human Exposure to Environmental Chemicals. Centers for Disease Control and Prevention Department of Health and Human Services. Available: http://wwwcdcgov/exposurereport Accessed 2011 February 25.
5. **Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, et al.** (2012) Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environ Health Perspect 120: 290–5.
6. **Kato K, Silva MJ, Reidy JA, Hurtz D 3rd, Malek NA, et al.** (2004) Mono(2-ethyl-5-hydroxyhexyl) phthalate and mono-(2-ethyl-5-oxohexyl) phthalate as biomarkers for human exposure assessment to di-(2-ethylhexyl) phthalate. Environ Health Perspect 112: 327–30.
7. **Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM** (2004) Temporal variability of urinary phthalate metabolite levels in men of reproductive age. Environ Health Perspect 112: 1734–40.
8. **Teitelbaum SL, Britton JA, Calafat AM, Ye X, Silva MJ, et al.** (2008) Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. Environ Res 106: 257–69.
9. **Adibi JJ, Whyatt RM, Williams PL, Calafat AM, Camann D, et al.** (2008) Characterization of Phthalate Exposure among Pregnant Women Assessed by Repeat Air and Urine Samples. Environ Health Perspect 116: 467–73.
10. **Kim Y, Ha EH, Kim EJ, Park H, Ha M, et al.** (2011) Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. Environ Health Perspect 119: 1495–500.
11. **Li Y, Zhuang M, Li T, Shi N** (2009) Neurobehavioral toxicity study of dibutyl phthalate on rats following in utero and lactational exposure. J Appl Toxicol 29: 603–11.

12. **Boberg J, Christiansen S, Axelstad M, Kledal TS, Vinggaard AM, et al.** (2011) Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats. Reprod Toxicol 31: 200–9.

13. **Cho SC1, Bhang SY, Hong YC, Shin MS, Kim BN, et al.** (2010) Relationship between environmental phthalate exposure and the intelligence of school-age children. Environ Health Perspect 118: 1027–32.

14. **Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, et al.** (2003) Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect 111: 201–5.

15. **Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, et al.** (2004) Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environ Health Perspect; 112: 331–8.

16. **Wechsler D** (2003) Wechsler Intelligence Scale for Children, 4th edition. San Antonio, TX: Psychological Corporation.

17. **Rauh V, Arunajadai S, Horton M, Perera F, Hoepner L, et al.** (2011) Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect 119: 1196–201.

18. **Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, et al.** (2011) Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect 119: 1189–95.

19. **Jusko TA, Henderson CR, Lanphear BP, Cory-Slechta DA, Parsons PJ, et al.** (2008) Blood lead concentrations $<$10 microg/dL and child intelligence at 6 years of age. Environ Health Perspect 116: 243–8.

20. **Dohrenwend BS, Krasnoff L, Askenasy AR, Dohrenwend BP** (1978) Exemplification of a method for scaling life events: the Peri Life Events Scale. J Health Soc Behav 19: 205–29.

21. **Brown L, Sherbenou RJ, Johnson SK** (1990) Test of Non-verbal Intelligence: A language-Free Measure of Cognitive Ability. Austin, TX: PRO-ED.

22. **Caldwell BM, Bradley RH** (1979) Home observation for measurement of the environment. Little Rock: University of Arkansas Press.

23. **Hornung RW, Reed DL** (1990) Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 5: 46–51.

24. **Engel SM, Zhu C, Berkowitz GS, Calafat AM, Silva MJ, et al.** (2009) Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. Neurotoxicology 30: 522–8.

25. **Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, et al.** (2011) Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol 33: 558–66.

26. **Téllez-Rojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K, et al.** (2013) Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. Sci Total Environ 461–462: 386–90.

27. **Zota AR, Calafat AM, Woodruff TJ** (2014) Temporal trends in phthalate exposures: Findings from the National Health and Nutrition Examination Survey, 2001–2010. Environ Health Perspect 122: 235–41.

28. **Weiss B** (2012) The intersection of neurotoxicology and endocrine disruption. Neurotoxicology 33: 1410–1419.

29. **Wolstenholme JT, Rissman EF, Connelly JJ** (2011) The role of Bisphenol A in shaping the brain, epigenome and behavior. Horm Behav 59: 296–305.

30. **Howdeshell KL, Wilson VS, Furr J, Lambright CR, Rider CV, et al.** (2008) A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague Dawley rat in a cummulative, dose additive manner. Toxicological Sciences 105: 153–165.

31. **Andrade AJ, Grande SW, Talsness CE, Grote K, Chahoud I** (2006) A dose-response study following in utero and lactational exposure to di-(2-ethylhexyl)-phthalate (DEHP): non-monotonic dose-response and low dose effects on rat brain aromatase activity. Toxicology 227: 185–192.

32. **Bonefeld-Jorgensen EC, Long M, Hofmeister MV, Vinggaard AM** (2007) Endocrine-disrupting potential of bisphenol A, bisphenol A dimethacrylate, 4-n-nonylphenol, and 4-n-octylphenol in vitro: new data and a brief review. Environ Health Perspect 115 Suppl 1:: 69–76.

33. **Breous E, Wenzel A, Loos U** (2005) The promoter of the human sodium/iodide symporter responds to certain phthalate plasticisers. Mol Cell Endocrinol 244: 75–78.

34. **Hinton RH, Mitchell FE, Mann A, Chescoe D, Price SC, et al.** (1986) Effects of phthalic acid esters on the liver and thyroid. Environ Health Perspect 70: 195–210.

35. **Howarth JA, Price SC, Dobrota M, Kentish PA, Hinton RH** (2001) Effects on male rats of di-(2-ethylhexyl) phthalate and di-n-hexylphthalate administered alone or in combination. Toxicol Lett 121: 35–43.

36. **O'Connor JC, Frame SR, Ladics GS** (2002) Evaluation of a 15-day screening assay using intact male rats for identifying steroid biosynthesis inhibitors and thyroid modulators. Toxicol Sci 69: 79–91.

37. **Sugiyama S, Shimada N, Miyoshi H, Yamauchi K** (2005) Detection of thyroid system-disrupting chemicals using in vitro and in vivo screening assays in Xenopus laevis. Toxicol Sci 88: 367–374.

38. **Boas M, Frederiksen H, Feldt-Rasmussen UF, Skakkebaek NE, Hegedus L, et al.** (2010) Childhood exposure to phthalates: association with thyroid function, insulin-like growth factor I, and growth. Environ Health Perspect 118: 1458–1464.

39. **Meeker JD, Calafat AM, Hauser R** (2007) Di(2-ethylhexyl) phthalate metabolites may alter thyroid hormone levels in men. Environ Health Perspect 115: 1029–1034.

40. **Meeker JD, Calafat AM, Hauser R** (2010) Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Technol 44: 1458–1463.

41. **Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, et al.** (2002) Thyroid hormone action is disrupted by bisphenol A as an antagonist. J Clin Endocrinol Metab 87: 5185–5190.

42. **Matsuda S, Matsuzawa D, Ishii D, Tomizawa H, Sutoh C, et al.** (2012) Effects of perinatal exposure to low dose of bisphenol A on anxiety like behavior and dopamine metabolites in brain. Prog Neuropsychopharmacol Biol Psychiatry 39: 273–279.

43. **Tanida T, Warita K, Ishihara K, Fukui S, Mitsuhashi T, et al.** (2009) Fetal and neonatal exposure to three typical environmental chemicals with different mechanisms of action: mixed exposure to phenol, phthalate, and dioxin cancels the effects of sole exposure on mouse midbrain dopaminergic nuclei. Toxicol Lett 189: 40–47.

44. **Genro JP, Kieling C, Rohde LA, Hutz MH** (2010) Attention-deficit/hyperactivity disorder and the dopaminergic hypotheses. Expert Rev Neurother 10: 587–601.

PLOS ONE

RESEARCH ARTICLE

Air Pollution and Stillbirth Risk: Exposure to Airborne Particulate Matter during Pregnancy Is Associated with Fetal Death

Emily DeFranco[1,2]*, Eric Hall[1], Monir Hossain[3], Aimin Chen[4], Erin N. Haynes[4], David Jones[3], Sheng Ren[5,6], Long Lu[6], Louis Muglia[1,2]

1 Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America, **2** Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America, **3** Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America, **4** Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America, **5** Department of Mathematics, University of Cincinnati, Cincinnati, Ohio, United States of America, **6** Division of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America

* emily.defranco@uc.edu

OPEN ACCESS

Citation: DeFranco E, Hall E, Hossain M, Chen A, Haynes EN, Jones D, et al. (2015) Air Pollution and Stillbirth Risk: Exposure to Airborne Particulate Matter during Pregnancy Is Associated with Fetal Death. PLoS ONE 10(3): e0120594. doi:10.1371/journal.pone.0120594

Academic Editor: Qinghua Sun, The Ohio State University, UNITED STATES

Received: August 12, 2014

Accepted: January 24, 2015

Published: March 20, 2015

Data Availability Statement: All relevant data are within the paper.

Funding: This work was supported by the Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, and March of Dimes Grant 22-FY13-543. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: One of the co-authors of this manuscript, AC, is a PLOS ONE Editorial Board

Abstract

Objective

To test the hypothesis that exposure to fine particulate air pollution ($PM_{2.5}$) is associated with stillbirth.

Study Design

Geo-spatial population-based cohort study using Ohio birth records (2006-2010) and local measures of $PM_{2.5}$, recorded by the EPA (2005-2010) via 57 monitoring stations across Ohio. Geographic coordinates of the mother's residence for each birth were linked to the nearest $PM_{2.5}$ monitoring station and monthly exposure averages calculated. The association between stillbirth and increased $PM_{2.5}$ levels was estimated, with adjustment for maternal age, race, education level, quantity of prenatal care, smoking, and season of conception.

Results

There were 349,188 live births and 1,848 stillbirths of non-anomalous singletons (20-42 weeks) with residence $\leq$10 km of a monitor station in Ohio during the study period. The mean $PM_{2.5}$ level in Ohio was 13.3 μg/m^3 [±1.8 SD, IQR(Q1: 12.1, Q3: 14.4, IQR: 2.3)], higher than the current EPA standard of 12 μg/m^3. High average $PM_{2.5}$ exposure through pregnancy was not associated with a significant increase in stillbirth risk, $_{adj}$OR 1.21(95% CI 0.96,1.53), nor was it increased with high exposure in the 1st or 2nd trimester. However, exposure to high levels of $PM_{2.5}$ in the third trimester of pregnancy was associated with 42% increased stillbirth risk, $_{adj}$OR 1.42(1.06,1.91).

member. This does not alter the authors' adherence to PLOS ONE Editorial policies and criteria.

Conclusions

Exposure to high levels of fine particulate air pollution in the third trimester of pregnancy is associated with increased stillbirth risk. Although the risk increase associated with high $PM_{2.5}$ levels is modest, the potential impact on overall stillbirth rates could be robust as all pregnant women are potentially at risk.

Introduction

The stillbirth rate (fetal death ≥20 weeks of gestation) is higher in the US compared to many developed countries. [1,2] The US stillbirth rate in 2006 was 6.0 per 1000 births,[3] almost 50% higher than the Healthy People 2010 goal of 4.1 per 1000.[4] The rate is higher in Ohio (6.2 per 1000) and further increased in the city of Cincinnati (6.9 per 1000), one of the most populous areas of the state. A variety of pre-existing medical, socioeconomic, prenatal, genetic, and environmental factors influence a woman's individual risk of stillbirth.

Exposure to harmful environmental pollutants is associated with adverse health outcomes and pregnancy complications.[5,6] Airborne particulate matter (PM) is a complex mixture of extremely small particles and liquid droplets including acids, organic chemicals, metals, and soil or dust particles. The smallest particles easily pass into the lungs and have the highest potential to negatively affect multiple organ systems. $PM_{2.5}$, fine particulate matter, measures <2.5 μm in aerodynamic diameter. The US Environmental Protection Agency (EPA) has air quality standards for particle pollution, and monitors local levels via stationary monitoring stations throughout the US. The US EPA National Ambient Air Quality Standard (NAAQS) for annual mean level of $PM_{2.5}$ is currently 12 $\mu g/m^3$.[7]

Few prior studies have reported the association between air pollutants and stillbirth,[8–13] and only two have assessed high exposure to $PM_{2.5}$ specifically and reported no significant association.[14,15] Previous studies have been limited in design by exposures with measures at a single time point or with a lack of geographic granularity, and lack thorough adjustment for important clinical or socio-demographic risk factors. In this study we aim to integrate air quality measures from statewide monitoring stations with vital records to perform geospatial analyses testing the hypothesis that exposure to fine particles in the air ($PM_{2.5}$) is associated with stillbirth risk.

Materials and Methods

Study design

Geo-spatial population-based cohort study using Ohio state birth records (2006–2010) and local measures of $PM_{2.5}$, recorded by the US Environmental Protection Agency (2005–2010) via 57 monitoring stations across Ohio.

Exposure

The primary exposure was high level of airborne $PM_{2.5}$, fine particulate matter in the air measuring <2.5 μm in diameter. High exposure was defined as ≥ mean $PM_{2.5}$ level plus interquartile range for the specific time period measured for each birth.

Outcome

The primary outcome was stillbirth. Stillbirth is recorded through vital records in the US using the definition of fetal death per the World Health Organization: birth of a fetus with no evidence of life such as movement, breathing, or heartbeat, irrespective of the duration of gestation and which is not an induced termination of pregnancy.[16] As is commonly recommended, we considered only stillbirths with birth weight $\geq$350 grams and occurring at $\geq$20 weeks of gestation for this analysis.[17] The reference group for comparison was comprised of live births also with birth weight $\geq$350 grams and occurring at $\geq$20 weeks of gestation. Gestational age was defined by the best obstetric estimate variable in the birth record, which combines last menstrual period and ultrasound parameters, as is commonly accepted in clinical practice for gestational age estimation.

Study population

All live births and stillbirths that occurred in Ohio during the 5 year study period, 2006–2010. The study cohort was limited to singleton births occurring at 20–42 weeks of gestation without known major congenital anomalies, and with mother's residence within 10 km of a $PM_{2.5}$ monitoring station. All live birth and stillbirth data were obtained from the Ohio Department of Health vital statistics database.

Statistical analyses

Daily measures of $PM_{2.5}$, recorded by 57 monitoring stations across the state of Ohio, were obtained from the Environmental Protection Agency from 2005–2010[18] and monthly averages of $PM_{2.5}$ were calculated for each station. Using geographic coordinates of the mother's residence for each birth and ArcGIS 10.1 (ESRI, Redlands, CA) software, vital records were linked to data from the nearest $PM_{2.5}$ monitoring station. Average $PM_{2.5}$ exposure level per trimester was calculated for each birth occurring within 10 km of a monitoring station.

Demographic, medical and delivery characteristics of stillbirths were compared to live births using t-test for continuous variable comparisons and χ^2 tests for categorical variables. The association between stillbirth risk and high $PM_{2.5}$ levels was estimated using generalized estimating equation (GEE) model with logit link function, with adjustment for maternal age, race, education level, quantity of prenatal care, cigarette smoking—each as recorded in the birth certificate, as well as season of conception which was created from the date of birth and gestational age at birth. There was minimal missing data for maternal residential address (2.3%), less than 0.1% missing maternal age or smoking status, 0.8% missing maternal race, 27.2% missing data prenatal care initiation, and 0.9% missing data on maternal educational level. There was a higher amount of missing data number of cigarettes smoked per day for smokers with stillbirth (31% missing), and therefore the dichotomous smoking status (yes/no) with minimal missing data ($<$0.01%) was utilized for analyses rather than modeled as a continuous variable. An exchangeable correlation matrix for the monitoring stations was used in the GEE models to account for spatial correlation within the same $PM_{2.5}$ monitor. Analyses were performed for births with residence within 10 km of a monitoring station, and then repeated as a sensitivity analysis limited to those with residence within 5 km of a monitoring station.

Analyses were performed using SAS version 9.3, SAS Institute Inc., Cary, NC, USA. Attributable risk (AR) was calculated using the formula: AR = Ie—Iu, where Ie = incidence of stillbirth in the high exposure group and Iu = incidence of stillbirth in the unexposed group. The population attributable risk (PAR), the reduction in stillbirth incidence that would be observed if the population were unexposed to high $PM_{2.5}$ levels, compared with its current (actual) exposure pattern was calculated as: PAR = Ip—Iu, where Ip is the population incidence. Population attributable

risk percentage (PAR%) was calculated as: PAR% = 100 x Pe (RR—1)/(Pe(RR-1)+1), where Pe is percentage of high exposure in the entire population (approximately 10% for the population included in this study) and RR is relative risk.

Stillbirth rates are reported as number of stillbirths per 1000 total births (live births plus stillbirths). Comparisons with a probability value <0.05 or 95% confidence interval without inclusion of the null were considered statistically significant.

The Ohio Department of Health and Human Subjects Institutional Review Board approved the protocol for this study. This study was exempt from review by the Institutional Review Board at the University of Cincinnati, Cincinnati, Ohio. A de-identified data set generated from vital records of all live births and stillbirths that occurred in the state from 2006–2010 was provided for this analysis by the Ohio Department of Health.

Results

There were 751,123 live births and 4,622 stillbirths in Ohio during the 5 year study period. We focused this analysis on singleton births occurring at 20–42 weeks of gestation without major congenital anomalies. The measurement of association between $PM_{2.5}$ levels and stillbirth was limited to births to mothers whose residence was within 10 km of a $PM_{2.5}$ monitoring station, resulting in a study sample of 351,036 births: 1,848 stillbirths and 349,188 live births, Fig. 1.

In the cohort studied in this analysis, the stillbirth rate decreased during the study period, from 5.7 per 1000 in 2006 to 4.6 per 1000 births in 2010, Table 1. The rate of stillbirth was higher in very urban areas, 5.4 per 1000, compared to residence in any less urban area, 4.3 per 1000. Most births analyzed (98%) occurred in very urban areas, where most monitoring stations are located and exposure levels are likely to be highest. Stillbirth rates were high among the oldest mothers, age $\geq$40 years, 11.6 per 1000, and non-Hispanic black mothers, 8.6 per 1000, as well as women with lower education level and tobacco use. Women with no prenatal care had the highest rate of stillbirth, 9.4 per 1000. Season of conception had no influence of stillbirth rates.

Continuous variables are presented as median (IQR) for non-normally distributed data and mean +/- standard deviation for normally distributed data.

Stillbirths occurred more frequently at 20–24 weeks (34.4%), compared to 25–28 weeks (15.1%), 29–32 weeks (13.9%), 33–36 weeks (18.1%) and term $\geq$37 weeks (18.4%), Table 2.

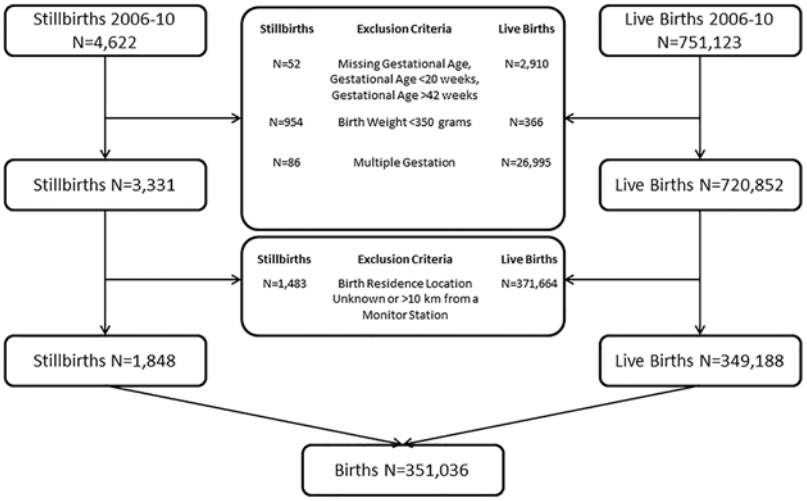


Fig 1. Flow diagram of the study population, Ohio births 2006–2010.

doi:10.1371/journal.pone.0120594.g001

Table 1. Maternal Characteristics, Ohio Birth Cohort 2006–2010.

Demographic Factors				
Advanced maternal age				
35–39 years	12.6	10.2	<0.01	6.5
≥ 40 years	2.7	1.2	<0.01	11.6
Race and Ethnicity				
Non Hispanic White	44.8	63.6	<0.01	3.7
Non Hispanic Black	46.8	28.3	<0.01	8.6
Hispanic	5.8	5.3	0.41	5.7
Other	2.7	2.8	0.83	5.1
Social Behaviors & Socioeconomic Factors				
Education				
Less than high school	23.4	20.3	<0.01	5.7
High school graduate	38.7	25.5	<0.01	7.5
College education	38.0	54.2	<0.01	3.5
Tobacco use	25.0	19.4	<0.01	6.4
Prenatal Care Initiation				
First trimester	78.7	67.9	<0.01	7.5
Second trimester	13.1	23.8	<0.01	3.6
Third trimester	3.1	4.9	<0.01	4.1
No prenatal care	5.0	3.4	<0.01	9.4
Year of Birth				
2006	22.2	20.5	0.07	5.7
2007	20.4	20.5	0.98	5.3
2008	20.4	20.2	0.81	5.3
2009	20.1	19.7	0.66	5.4
2010	16.8	19.1	0.01	4.6
Season				
Winter	25.1	24.8	0.76	5.3
Spring	23.8	24.6	0.39	5.1
Summer	25.4	25.1	0.75	5.3
Fall	25.8	25.5	0.81	5.3

Dichotomous variables for first 2 columns are presented as percent of total for each characteristic. Stillbirth rate is presented as number of stillbirths per 1000 total births per each characteristic.

doi:10.1371/journal.pone.0120594.t001

The stillbirth rate was lowest for births at term, 1.1 per 1000. Considering that a major contributor to stillbirth rates is intrapartum death of a previable or periviable fetus born between 20–24 weeks due to preterm labor, the rate of stillbirth in the 20–24 week gestational age period was highest, as expected, 365.7 per 1000.

The mean $PM_{2.5}$ level during the study period (2006–2010) in Ohio was 13.3 $\mu g/m^3$ [±1.8 $\mu g/m^3$, IQR (Q1: 12.1, Q3: 14.4, IQR: 2.3)], which is higher than The US EPA National Ambient Air Quality Standard (NAAQS) of 12 $\mu g/m^3$.[7] Mean $PM_{2.5}$ level, IQR for the entire cohort per trimester was: 1st trimester 13.67, 3.53 $\mu g/m^3$; 2nd trimester 13.30, 2.96 $\mu g/m^3$; 3rd trimester 13.05, 3.17 $\mu g/m^3$; pregnancy average 13.32, 2.35 $\mu g/m^3$. High $PM_{2.5}$ level was defined as mean + IQR for each group: 1st trimester 17.2 $\mu g/m^3$; 2nd trimester 16.26 $\mu g/m^3$; 3rd trimester 16.22 $\mu g/m^3$; pregnancy average 15.67 $\mu g/m^3$.

The mean $PM_{2.5}$ levels during first trimester of pregnancy were not significantly different for stillbirths compared to the live birth group However, mean $PM_{2.5}$ levels during the second

Table 2. Birth Characteristics, Ohio 2006–2010.

Birth weight, grams				
350–2499	78.9	7.7	<0.01	48.1
2500–3999	18.7	84.7	<0.01	1.1
≥4000	2.4	7.6	<0.01	1.6
Gestational age at birth,weeks				
20–24	34.4	0.3	<0.01	365.7
25–28	15.2	0.6	<0.01	121.7
29–32	13.9	1.2	<0.01	59.0
33–36	18.1	7.3	<0.01	12.9
≥37	18.4	90.7	<0.01	1.1

Dichotomous variables for first 2 columns are presented as percent of total for each category. Stillbirth rate is presented as number of stillbirths per 1000 total births per each category.

doi:10.1371/journal.pone.0120594.t002

trimester were slightly lower and during the third trimester were significantly higher for the stillbirth group compared to the live birth group, see Table 3. Overall, pregnancy average $PM_{2.5}$ levels for the entire cohort did not significantly differ between stillbirths and live births, 13.40 ± 1.9 μg/m^3 versus 13.32 ± 1.75 μg/m^3, p = 0.09. We identified significant correlations between $PM_{2.5}$ and exposure levels of several other airborne measures of pollutants ($p<0.001$) including nitrogen dioxide, sulfur dioxide, ozone, carbon monoxide and lead.

When analyzing the outcomes for births within 10 km of a stationary monitor, exposure to high levels of $PM_{2.5}$ throughout the pregnancy was not associated with a significant increase in stillbirth risk, $_{adj}$OR 1.21 (95% CI 0.96, 1.53). Likewise, the risk was not increased with exposure to high $PM_{2.5}$ levels in the 1st trimester, $_{adj}$OR 0.77 (95% CI 0.58, 1.02), or 2nd trimester $_{adj}$OR 0.80 (95% CI 0.62, 1.04). However, exposure to high levels of $PM_{2.5}$ in the third trimester of pregnancy was associated with 42% increased stillbirth risk, $_{adj}$OR 1.42 (95% CI 1.06, 1.91), even after adjustment for important coexisting risk factors for fetal death, Fig. 2. Sensitivity analyses performed using a more strict residential distance-to-monitor cut-off of 5 km demonstrated similar findings. The 5 km cut-off associations demonstrated no difference in stillbirth risk with high $PM_{2.5}$ levels throughout pregnancy or in the second trimester compared to live births. There was minimally decreased stillbirth odds with high 1st trimester exposure. Compared to the 10 km cut-off analysis, there was a slightly more robust effect size of stillbirth odds with high 3rd trimester $PM_{2.5}$ exposure, adjusted OR 1.54 (95% CI 1.08, 2.20), see Table 4. However, if $PM_{2.5}$ exposure was modeled as a continuous variable rather than a dichotomous variable, this finding became non-significant. The relative influence of important coexisting risk factors included in the adjusted analysis of $PM_{2.5}$ exposure and stillbirth risk is depicted in Table 4.

Table 3. $PM_{2.5}$ levels in Ohio 2006–2010, by trimester of exposure in pregnancy.

$PM_{2.5}$ level	Mean (SD)	IQR (Q3, Q1)	Mean (SD)	IQR (Q3, Q1)	
First trimester	13.60 (2.76)	15.04, 11.72	13.67 (2.87)	15.22, 11.69	0.380
Second trimester	13.18 (2.26)	14.63, 11.59	13.30 (2.36)	14.66, 11.70	0.026
Third trimester	13.24 (2.76)	14.95, 11.29	13.05 (2.34)	14.57, 11.40	0.049
Entire pregnancy	13.32 (1.81)	14.44, 12.07	13.32 (1.75)	14.40, 12.05	0.870

$PM_{2.5}$ levels are expressed as mean air concentration in μg/m^3. SD = standard deviation, IQR = interquartile range (3rd, 1st quartile).

doi:10.1371/journal.pone.0120594.t003

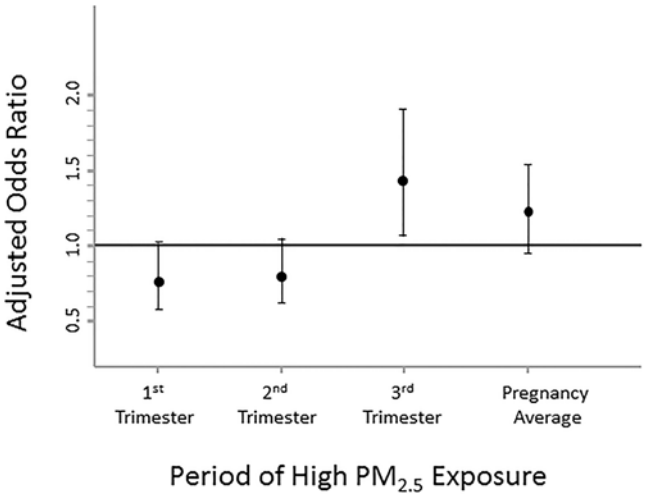


Fig 2. Relative odds of stillbirth associated with exposure to high levels of $PM_{2.5}$, by trimester of pregnancy, Ohio 2006–2010.

doi:10.1371/journal.pone.0120594.g002

The attributable risk of stillbirth related to high $PM_{2.5}$ exposure (7.48 per 1000 minus 5.2 per 1000) was 2.2 per 1000. The attributable risk percent: (Ie-Iu)/Ie is 30%, i.e. for the exposed population, 30% of stillbirths were from high $PM_{2.5}$ exposure. Assuming 10% of population was exposed to high $PM_{2.5}$, the population attributable risk percentage of high $PM_{2.5}$ exposure is 4% for stillbirth.

Discussion

Main findings

In this study we found that exposure to high levels of fine particulate air pollution, $PM_{2.5}$, in the third trimester of pregnancy is associated with increased stillbirth risk. Despite adjustment for important coexisting risk factors for fetal death such as maternal age, race, tobacco use and lack of prenatal care, we found that pregnant women exposed to high levels of $PM_{2.5}$ during the third trimester of pregnancy had a 42% increased risk of stillbirth. This is a novel finding that has not previously been reported.

Strengths and limitations

One significant limitation of this study, and most studies of air pollution on heath complications, is the approach of measuring quantity of exposure through stationary monitor sites. Although these represent a good estimation of hourly, daily, or longer duration average regional air pollution levels, they do not account for variations in personal exposure levels or amount of variation of indoor air quality. This approach also does not take into consideration variations in pollutant levels throughout the geographic metric included in the analysis, which was a 10 km radius from the monitor station in this study, nor is there any adjustment for possible geographic mobility throughout the pregnancy. However, the rate of residential mobility has been estimated to be fairly low, approximately 12% during pregnancy, and the majority of those who do move stay within the same municipality.[19] There is also the possibility of interaction with other concomitant pollutant exposures or unmeasured sociodemographic and pregnancy risks for stillbirth, which could possibly cluster in areas with high pollutant levels. We identified significant correlations between exposure levels of $PM_{2.5}$ and several other airborne pollutants ($p<0.001$) including nitrogen dioxide, sulfur dioxide, ozone, carbon monoxide and lead.

Table 4. Logistic regression of factors associated with stillbirth, Ohio 2006–2010.

Maternal Age, years		
<20	1.03 (0.80, 1.32)	1.11 (0.85, 1.44)
20–24	0.95 (0.78, 1.15)	0.89 (0.72, 1.10)
25–29	1.00 (Referent)	1.00 (Referent)
30–34	1.11 (0.90, 1.37)	1.00 (0.76, 1.33)
35–39	1.56 (1.25, 1.96)	1.35 (1.07, 1.30)
≥40	2.80 (1.86, 4.21)	2.24 (1.34, 3.75)
Maternal Race		
Non-Hispanic white	1.00 (Referent)	1.00 (Referent)
Non-Hispanic black	2.31 (0.99, 5.40)	1.05 (0.46, 2.41)
Hispanic	1.63 (1.04, 2.57)	1.13 (0.57, 2.21)
Other Non-Hispanic	1.39 (0.92, 2.09)	0.87 (0.52, 1.44)
Maternal Education Level		
Less than high school	1.77 (1.29, 2.44)	1.77 (1.37, 2.28)
High school only	2.26 (1.89, 2.71)	2.22 (1.76, 2.80)
Postsecondary education	1.00 (Referent)	1.00 (Referent)
Prenatal Care Initiation		
First trimester	1.00 (Referent)	1.00 (Referent)
Second trimester	0.34 (0.27, 0.43)	0.39 (0.30, 0.49)
Third trimester	0.32 (0.21, 0.48)	0.30 (0.21, 0.45)
No prenatal care	0.70 (0.40, 1.22)	0.78 (0.49, 1.26)
Season of conception		
Winter	1.07 (0.89, 1.29)	1.09 (0.89, 1.32)
Spring	1.00 (Referent)	1.00 (Referent)
Summer	1.13 (0.94, 1.37)	1.15 (0.90, 1.47)
Fall	1.09 (0.91, 1.30)	1.14 (0.98, 1.33)
Tobacco Use	1.44 (1.22, 1.71)	1.28 (1.02, 1.62)
High $PM_{2.5}$ Exposure		
Average over pregnancy**	1.21 (0.96, 1.53)	1.06 (0.80, 1.41)
First trimester	0.77 (0.58, 1.02)	0.71 (0.52, 0.96)
Second trimester	0.80 (0.62, 1.04)	0.78 (0.60, 1.02)
Third trimester	1.42 (1.06, 1.91)	1.54 (1.08, 2.20)

*Odds ratio estimates are adjusted for all other factors listed in the first column of the table.

** The odds ratios for all covariates in the table are derived from the logistic regression model of High $PM_{2.5}$ exposure average over pregnancy.

doi:10.1371/journal.pone.0120594.t004

However, the differing locations of these stationary monitors across the state of Ohio and fewer numbers of monitors for most pollutants compared to $PM_{2.5}$ monitors limited our capacity to accurately assess and adjust for high levels of each other pollutant in women who resided within 5 or 10 km of a stationary $PM_{2.5}$ monitor. Despite this, using individual pollutant-specific stationary monitors to quantify an individual's air pollution exposure is a commonly used and accepted quality approach of assessing the association between air pollution and birth outcomes.[20–25] Although we did adjust for the most commonly known risk factors for stillbirth, other unmeasured factors could have also influenced our findings and may even explain the positive associations identified, considering the small effect sizes and few significant findings in this study. Other commonly reported limitations of vital statistics data used for research is related to accuracy of the data. Certainly, the choice of variables for analysis affects the study's internal validity. In this study, stillbirth and live birth are reported in the same way as they are

throughout the US, with reliable certainty. Our exposure levels should be reliably estimated as well, as data was obtained directly from daily measures reported by the US EPA.[18] Demographic factors such as maternal age and race are felt to be quite accurate in birth records, and the accuracy of gestational age of birth is considered reliable with a relatively narrow margin of variability in birth certificates as well.[26] Other variables on birth records are known to be underreported, such as ante- and intrapartum complications and co-morbid conditions such as hypertension and diabetes;[27] however, the primary exposure and outcome in this study did not include variables likely to have significant data accuracy concerns. Inability to adjust thoroughly for concomitant medical risk factors could have biased our results toward a positive association, however other design limitations may have biased toward the null.

Our study also has significant strengths compared to other studies on air pollution and pregnancy complications. Our cohort design and time-based approach considering cumulative daily-monthly pollutant levels and assignment to specific time periods of pregnancy by trimester enabled us to assess which time during fetal development may be the most susceptible to high levels of air pollution. In addition, we utilized data on specific location of residence of each birth in the state and were able to assign accurate regional, temporal exposure levels to each live birth and stillbirth. Furthermore, we performed sensitivity analyses by repeating our analyses to births with home residence within a closer proximity to a stationary monitor, 5 km, and demonstrated consistency of effect. The non-significant association of stillbirth risk with high exposure in the third trimester found when analyzing $PM_{2.5}$ as a continuous variable in a sensitivity analysis, differing from the significant association when modeled as a categorical variable in our primary planned analysis, may indicate that there is a threshold above which exposure levels increase risk and may not at mid-range exposure levels, and perhaps not in a linear fashion. Our contemporary study cohort (2006–2010), and large population-based sample size (1,848 stillbirths and 349,188 live births) of US births further improved the external validity and generalizability of our findings. Our study is the largest cohort assessing the influence of $PM_{2.5}$ on stillbirth risk reported to date.

Interpretation

Differences in reported effects of airborne particulate matter on birth outcomes in the existing literature may be influenced by differences in populations studied.[8,10,12] Some countries have much higher levels of concomitant air pollution density and frequency of other exposures such as maternal tobacco smoking, as in Russia and Greece. In addition, prior study differences may be confounded by geographic location of study, as the composition of particulate matter differs by locale. In China, coal is the major component in particulate air pollution, whereas industrial waste contributes a majority in the Czech Republic, auto exhaust is the major source in South Korea, and dust is the major contributor in the US.[28] Furthermore, prior studies have reported associations with various sizes of airborne particulate matter including total suspended particulates (TSP) and inhalable course particulates <10 μm (PM_{10}) which can be found in dusty areas near roadways and some industries. Few studies have investigated fine particulate matter, $PM_{2.5,}$ which is comprised of smoke, haze, and gas emissions. These are the smallest particles in the air with the highest likelihood of being inhaled and subsequently entering the systemic circulation, ultimately causing negative health effects (http://www.epa.gov/airquality/particlepollution/health.html).[5,6]

Only two prior studies have assessed airborne $PM_{2.5}$ influences on stillbirth. Similar to our study, prior investigators (Faiz, et al), estimated the effect of trimester-specific exposures on stillbirth risk.[13] Despite similar study design and also using a population-based sample in the US (New Jersey), but from slightly older time period from 1998–2004, the authors reported a

non-significant association between increased $PM_{2.5}$ exposure in the third trimester and stillbirth, adjOR 1.08 (CI 0.79, 1.48). There are several explanations for the differences in study findings. Our study was significantly larger, by more than 50%, compared to the cohort included in the study by Faiz, et al, increasing our statistical power to detect a difference. The direction of effect in Faiz's study and our study were similar, both demonstrating a modest risk increase; however, our study demonstrated this as a significant finding with 95% confidence interval greater than the null. An additional explanation may be related to their designation of exposure quantity. In their study, stillbirth risk was measured as an interquartile range increase of $PM_{2.5}$ exposure, about 4 $\mu g/m^3$ increase. Our study compared the risk of stillbirth for those women within high $PM_{2.5}$ exposure, >16–17 $\mu g/m^3$, versus those with low exposure levels. Assuming that the highest exposure levels may have the most robust effect on adverse outcome, our choice of exposure characterization may have enhanced our power to detect a difference. A more recent study published by the same authors, Faiz et. al (2013), also found no significant association between increased $PM_{2.5}$ exposure, measured per quartile increase, and stillbirth when quantified as high levels in the immediate few days prior to birth, despite similarly studying a population exposed to high mean levels of $PM_{2.5}$ (mean exposure levels 14.7–15.0 $\mu g/m^3$). [15] Several other studies have analyzed other forms of airborne particulate matter, total suspended particles (TSP) [10] and course particles (PM_{10}) [8,12] and found no association with stillbirth, however exposure to larger airborne particles may have a different mechanism of action, or be less influential with regards to negative health effects.[6]

The mechanism by which particulate air pollution might negatively affect the fetus through maternal exposure has not been clearly elucidated. The association between particulate air pollution and poor health outcomes in adults has been more definitively established.[6] In adults, three potential mechanisms of PM exposure have been proposed: stimulation of the inflammatory response resulting in increased coagulation, immune or allergic-type response, and autonomic effects on the cardiovascular system leading to decreased heart rate variability.[5] It is plausible that any or all of these mechanisms may contribute to alterations in uteroplacental perfusion, nutrient and oxygen transfer to the fetus, or even catastrophic thrombotic or ischemic events leading to abrupt fetal death.

The relative decrease in stillbirth risk with high levels of exposure in the first trimester of pregnancy, when analyses were limited to birth residences within a 5 km radius of a monitor (data displayed in Table 4), is in contrast to the direction of effect with high exposure later in pregnancy. The biologic explanation for this difference in stillbirth risk by timing of high $PM_{2.5}$ exposure in pregnancy is more difficult to postulate. These findings could be influenced by our study design, as only pregnancies progressing past 20 weeks were reliably captured as a birth in the vital statistics birth records, and included in the comparisons of stillbirth versus live birth risk. If high $PM_{2.5}$ exposure in the first and early second trimester had a robust effect on some particularly vulnerable early pregnancies, resulting in miscarriage, this may have resulted in an underrepresentation of pregnancies vulnerable to $PM_{2.5}$ exposure with high levels represented in the first trimester in this study. This could have biased risk estimates in those early pregnancy periods toward the null, or even appear protective. An additional hypothesis is there may be underlying pathophysiologic mechanisms by which an early inflammatory stimulus or hypercoagulable state might be protective later against pregnancy complications or other exposures that are known to lead to stillbirth.

Conclusion

Although the risk increase associated with exposure to high levels of $PM_{2.5}$ in the air is modest, the potential impact on overall stillbirth rates is robust as all pregnant women are potentially at

risk. This may contribute to the higher stillbirth rates in Ohio compared to other states in the US, especially in urban areas. Based on findings from this study, we estimate the attributable risk of exposure to high levels of airborne $PM_{2.5}$ pollution to be 0.22%. Otherwise stated, 2.2 stillbirths per 1000 may be attributed to increased exposure to $PM_{2.5}$ in Ohio in those with high $PM_{2.5}$ exposure. Assuming 10% of population was exposed to high particle pollution, the population attributable risk percentage of high exposure is 4% for stillbirth. These findings may indicate that improving air quality in the US could help to address the high stillbirth rate in our country, especially as compared to many other industrialized nations. [1,2]

Acknowledgments

Disclaimer

All of the analysis, interpretations, and conclusions that were derived from the data source and included in this article are those of the authors and not the Ohio Department of Health. Access to de-identified Ohio birth certificate data was provided by the Ohio Department of Health.

Presentation information

This study was presented as an oral presentation at the 2013 Annual Meeting of the Central Association of Obstetricians and Gynecologists, Oct. 16–19, 2013, Napa, CA

Author Contributions

Conceived and designed the experiments: ED DH MH AC ENH DJ LM. Performed the experiments: ED EH MH DJ SR LL. Analyzed the data: ED EH MH DJ SR LL. Contributed reagents/materials/analysis tools: ED EH MH AC DJ. Wrote the paper: ED EH MH AC ENH DJ LM SR LL.

References

1. Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. Lancet 2011; 377: 1319–30. doi: 10.1016/S0140-6736(10)62310-0 PMID: 21496917
2. World Health Organization website. County stillbirth rates per 1000 total births for 2009 | World Health Organization, Save the Children. Available: http://who.int/pmnch/media/news/2011/stillbirths_countryrates.pdf. Accessed 23 Dec 2013.
3. MacDorman MF, Kirmeyer S, Wilson EC. Fetal and Perinatal Mortality, United States, 2006. National Vital Statistics Reports, Vol. 60. No. 8; 2012. PMID: 24979970
4. Healthy People 2010 Home Page. Available: http://www.healthypeople.gov/2010/. Accessed 19 Dec 2013.
5. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: A systematic review of the epidemiologic evidence. Epidemiology 2004; 15:36–45. PMID: 14712145
6. Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. Long-term air pollution exposure and cardio-respiratory mortality: A review. Environmental Health: A Global Access Science Source 2013; 12.
7. United States Environmental Protection Agency website. National Ambient Air Quality Standards (NAAQS) | Air and Radiation. Available: http://epa.gov/air/criteria.html. Accessed 21 June 2014.
8. Pereira LAA, Loomis D, Conceição GMS, Braga ALF, Arcas RM, Kishi HS, et al. Association between air pollution and intrauterine mortality in sao paulo, brazil. Environ Health Perspect 1998; 106:325–9. PMID: 9618348
9. Landgren O. Environmental pollution and delivery outcome in southern sweden: A study with central registries. Acta Paediatrica, International Journal of Paediatrics 1996; 85:1361–4.
10. Bobak M, Leon DA. Pregnancy outcomes and outdoor air pollution: An ecological study in districts of the czech republic 1986–8. Occup Environ Med 1999; 56:539–43. PMID: 10492651

11. Vassilev ZP, Robson MG, Klotz JB. Outdoor exposure to airborne polycyclic organic matter and adverse reproductive outcomes: A pilot study. Am J Ind Med 2001; 40:255–62. PMID: 11598971
12. Hwang B-, Lee YL, Jaakkola JJK. Air pollution and stillbirth: A population-based case-control study in taiwan. Environ Health Perspect 2011; 119:1345–9. doi: 10.1289/ehp.1003056 PMID: 21447454
13. Pearce MS, Glinianaia SV, Rankin J, Rushton S, Charlton M, Parker L, et al. No association between ambient particulate matter exposure during pregnancy and stillbirth risk in the north of England, 1962–1992. Environ Res 2010; 110:118–22. doi: 10.1016/j.envres.2009.10.003 PMID: 19863953
14. Faiz AS, Rhoads GG, Demissie K, Kruse L, Lin Y, Rich DQ. Ambient air pollution and the risk of stillbirth. Am J Epidemiol 2012; 176:308–16. doi: 10.1093/aje/kws029 PMID: 22811493
15. Faiz AS, Rhoads GG, Demissie K, Lin Y, Kruse L, Rich DQ. Does ambient air pollution trigger stillbirth? Epidemiology 2013; 24:538–44. doi: 10.1097/EDE.0b013e3182949ce5 PMID: 23676263
16. US Department of Health and Human Services, Centers for Disease Control and Prevention website. National Center for Health Statistics, State Definitions and Reporting Requirements. 1997 revision edition. Available: http://www.cdc.gov/nchs/data/misc/itop97.pdf. Accessed 21 June 2014.
17. ACOG practice bulletin no. 102: Management of stillbirth. Obstet Gynecol 2009; 113:748–61. doi: 10.1097/AOG.0b013e31819e9ee2 PMID: 19300347
18. United States Environmental Protection Agency website. AirData. Available: http://www.epa.gov/airdata/. Accessed 21 June 2014.
19. Fell DB, Dodds L, King WD. Residential mobility during pregnancy. Paediatr Perinat Epidemiol. 2004; 18(6):408–14. PMID: 15535816
20. Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. Using new satellite based exposure methods to study the association between pregnancy $PM_{2.5}$ exposure, premature birth and birth weight in Massachusetts. Environ Health. 2012 Jun 18; 11:40. doi: 10.1186/1476-069X-11-40 PMID: 22709681
21. Padula AM, Tager IB, Carmichael SL, Hammond SK, Lurmann F, Shaw GM. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. Am J Epidemiol. 2013 May 15; 177(10):1074–85. doi: 10.1093/aje/kws367 PMID: 23538941
22. Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. Traffic-related air toxics and term low birth weight in Los Angeles County, California. Environ Health Perspect. 2012; 120(1):132–8. doi: 10.1289/ehp.1103408 PMID: 21835727
23. Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. Paediatr Perinat Epidemiol. 2012; 26 (2):91–100. doi: 10.1111/j.1365-3016.2011.01245.x PMID: 22324494
24. Mainolfi MB, Salihu HM, Wilson RE, Mbah AK. Low-level exposure to air pollution and risk of adverse birth outcomes in Hillsborough County, Florida. J Occup Environ Med. 2013; 55(5):490–4. doi: 10.1097/JOM.0b013e31828df013 PMID: 23618881
25. Rich DQ, Demissie K, Lu SE, Kamat L, Wartenberg D, Rhoads GG. Ambient air pollutant concentrations during pregnancy and the risk of fetal growth restriction. J Epidemiol Community Health. 2009; 63-(6):488–96. doi: 10.1136/jech.2008.082792 PMID: 19359274
26. Dietz PM, Bombard JM, Hutchings YL, Gauthier JP, Gambatese MA, Ko JY, et al. Validation of obstetric estimate of gestational age on US birth certificates. Am J Obstet Gynecol. 2014; 210(4):335 e331–335. doi: 10.1016/j.ajog.2013.10.875 PMID: 24184397
27. Reichman NE, Schwartz-Soicher O. Accuracy of birth certificate data by risk factors and outcomes: Analysis of data from New Jersey. Am J Obstet Gynecol 2007; 197:32.e1,32.e8. PMID: 17618747
28. United States Environmental Protection Agency website. State and County Emission Summaries | Air Emission Sources. Available: http://www.epa.gov/cgi-bin/broker?_service = data&_debug=0&_program = dataprog.national_1.sas&polchoice=PM. Accessed 21 June 2014.

PLOS | ONE

RESEARCH ARTICLE

Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania

Shaina L. Stacy[1], LuAnn L. Brink[2], Jacob C. Larkin[3], Yoel Sadovsky[3], Bernard D. Goldstein[1], Bruce R. Pitt[1]*, Evelyn O. Talbott[2]

1 Department of Environmental and Occupational Health, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **2** Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **3** Magee-Womens Research Institute and Department of Obstetrics, Gynecology and Reproductive Sciences, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

* brucep@pitt.edu

OPEN ACCESS

Citation: Stacy SL, Brink LL, Larkin JC, Sadovsky Y, Goldstein BD, Pitt BR, et al. (2015) Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania. PLoS ONE 10(6): e0126425. doi:10.1371/journal.pone.0126425

Academic Editor: Jaymie Meliker, Stony Brook University, Graduate Program in Public Health, UNITED STATES

Received: January 24, 2015

Accepted: April 2, 2015

Published: June 3, 2015

Data Availability Statement: Gas well data are publicly available from the Pennsylvania Department of Environmental Protection (website: http://www.portal.state.pa.us/portal/server.pt/community/oil_and_gas_reports/20297). Birth certificate data are considered to be protected health information since it contains personal identifiers, such as geocoded residences. Therefore, it cannot be made available in the manuscript, the supplemental files, or a public repository. The Pennsylvania Department of Health requires Institutional Review Board approval, and data access is password protected. However, readers

Abstract

Unconventional gas drilling (UGD) has enabled extraordinarily rapid growth in the extraction of natural gas. Despite frequently expressed public concern, human health studies have not kept pace. We investigated the association of proximity to UGD in the Marcellus Shale formation and perinatal outcomes in a retrospective cohort study of 15,451 live births in Southwest Pennsylvania from 2007–2010. Mothers were categorized into exposure quartiles based on inverse distance weighted (IDW) well count; least exposed mothers (first quartile) had an IDW well count less than 0.87 wells per mile, while the most exposed (fourth quartile) had 6.00 wells or greater per mile. Multivariate linear (birth weight) or logistical (small for gestational age (SGA) and prematurity) regression analyses, accounting for differences in maternal and child risk factors, were performed. There was no significant association of proximity and density of UGD with prematurity. Comparison of the most to least exposed, however, revealed lower birth weight (3323 ± 558 vs 3344 ± 544 g) and a higher incidence of SGA (6.5 vs 4.8%, respectively; odds ratio: 1.34; 95% confidence interval: 1.10–1.63). While the clinical significance of the differences in birth weight among the exposure groups is unclear, the present findings further emphasize the need for larger studies, in regio-specific fashion, with more precise characterization of exposure over an extended period of time to evaluate the potential public health significance of UGD.

Introduction

Unconventional gas development (UGD), characterized by advances in engineering, including horizontal drilling and high volume hydraulic fracturing, enables extraction of large amounts of fossil fuel from shale deposits at depths that were previously unapproachable [1]. In Pennsylvania, UGD in the Marcellus Shale formation has rapidly advanced from only 44 such wells

may direct inquiries and data access requests to: James Rubertone, Department of Health, Bureau of Health Statistics and Registries, 555 Walnut Street, 6th Floor, Harrisburg, PA 17101-1914, Phone: 717-547-3690, Fax: 717-772-3258, jrubertone@pa.gov.

Funding: This study was supported by the Heinz Endowments (website: http://www.heinz.org/) (BRP). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

known to be drilled before 2007 to 2,864 wells drilled during the 2007–2010 period of our study, and with continued rapid expansion to as many as 80,000 forecasted [2].

Several recent reviews summarizing the evolving UGD process describe the potential for adverse health effects and delineate challenges that have contributed to as yet minimal understanding of public health impact [1, 3–4]. UGD is a dynamic process encompassing preparation of the site, well development and production, the removal of wastes and the downstream distribution of gas [1]. The well is drilled vertically into a shale layer often 1.5 km underground and then turned laterally within the shale layer for another 2–3 km before holes are blown at intervals in the pipe. This is followed by the high-pressure injection of approximately 5 million gallons of water to hydraulically fracture the shale layer, allowing the release of gas tightly bound to the shale. Added to this water is a complex mixture, including approximately 15% of a physical agent (usually silica) to prop open the fractures and about 0.5–2.0% of an evolving mixture of about 6–10 chemicals (e.g., surfactants, biocides, metal chelators, and others), that enhance release and flow of the gas. Return or flowback fluids include mixtures of the hydrofracturing agents, hydrocarbon products (methane and other volatile organic hydrocarbons including benzene) and, of particular toxicological significance, naturally occurring agents dissolved from the shale bed (e.g., brine, radionuclides, arsenic, barium, strontium and other metals) [5–6]. Over a thousand diesel truck trips are usually required for site preparation, bringing hydrofracturing fluids and disposing of the approximately 1–2 million gallons of fluid that flows back from the well. In the western US, flowback fluids are generally rapidly disposed of in deep underground injection wells. Such wells are uncommon in Pennsylvania. UGD operators first discharged to publically owned treatment works, which treated the wastewater and discharged to the regional rivers until it was determined that this practice was associated with increasing concentrations of bromine and other contaminants in drinking water pulled from the rivers [7–8]. Next, the flowback waters were transported to deep underground injection wells in Ohio. However, the resultant mild earthquakes in Ohio have led to a variety of attempted solutions to deal with these flowback fluids on the surface, including impoundments and recycling, thereby increasing the opportunity for human exposure [9]. This continues to be the current situation in Pennsylvania. As flowback fluids also contain hydrocarbon product, they can be a source of air pollution. Esswein et al. recently reported that workers involved with waste fluids could be exposed to levels of benzene above allowable occupational health levels [10]. This is pertinent as benzene in air has been associated with adverse birth outcomes [11].

Wells can be hydrofractured intermittently on multiple occasions to stimulate product flow. A more continuous process of product development occurs in region-specific patterns. This includes condensate tanks and glycol dehydrators to separate dry (methane) and wet (higher carbons such as ethane) gas components of product and diesel fuel operated compressors (to liquefy gas for shipping via pipelines) [12]. As such, concern about air pollution is both direct (flaring of methane gas at well heads, controlled burning of natural gas and release of VOCs including benzene, toluene, ethylbenzene and xylene) and indirect (traffic, diesel operated compressors).

Major challenges in assessing and quantifying environmental, ecological and human health related effects (existing and potential) of UGD exist largely due to the dynamic and complex nature of the evolving UGD process itself as well as differences in geology between site locations, UGD technique and community demography. Together, these factors make it difficult to compare experiences, historically and concomitantly, within and between regional efforts. Several recent studies have provided measurements of likely pollutants, focusing on hydrocarbons found in air [13] or on thermogenic methane found in shallow drinking water sources [12, 14–15]. A study in Colorado revealed that those living within 0.5 miles of a well were exposed to

air pollutant levels, including benzene, that significantly increased non-cancer risk [16]. However, there is still a lack of information linking potential exposures with public health risks, which led the State of New York to the following declaration: "Until the science provides sufficient information to determine the level of risk to public health from HVHF and whether the risks can be adequately managed, HVHF should not proceed in New York State" [17].

The embryo/fetus is particularly sensitive to the effects of environmental agents [18]. A host of environmental and behavioral risk factors have been identified and linked to low birth weight and prematurity. They include most notably cigarette smoking [19–20], maternal occupational exposures to metals [21–22], and recently $PM_{2.5}$ and ozone [13, 23–24]. The mechanism is thought to be one involving oxidative stress or inflammation [25]. Xu et al. have noted a relationship in southwestern Pennsylvania of low birth weight and $PM_{2.5}$ [23]. The strength of using birth outcomes is the availability of data and the ability to capture the critical time of exposure and linkage to outcomes within the nine month period [26]. McKenzie et al. used a retrospective cohort design and exposure estimates from an inverse distance weighted (IDW) approach to explore associations between maternal residential proximity to hydraulic fracturing sites in Colorado and birth outcomes [27]. They found an increase in the prevalence of congenital heart defects and, to a lesser extent, neural tube defects with increasing exposure to natural gas extraction. They also found an increase in birth weight associated with well density.

We adapted the epidemiological and geographic information systems (GIS) approaches of McKenzie et al. [27] to explore the potential effects of UGD on infants born to mothers living in Southwestern PA where unconventional drilling of the Marcellus Shale has been rapidly expanding. The objective of the present study is to use readily available data on birth outcomes for Southwestern Pennsylvania to investigate the relationship of proximity to UGD and perinatal outcomes for 2007 to 2010.

Methods

Natural gas well and birth data were collected for Butler, Washington and Westmoreland counties in PA for the years 2007 to 2010. The UGD locations were obtained from the Pennsylvania Department of Environmental Protection (PADEP), that defines UGD as wells having both a lateral component and hydraulic fracturing, a process relatively new to Pennsylvania until 2005 [2]. The PADEP dataset also includes information on drilling commencement dates, known as the SPUD date, and well status (active, abandoned, etc.) [2]. Birth data for these counties were obtained using information from birth certificates, which had also been geocoded by the Pennsylvania Department of Health (PADOH) Bureau of Vital Statistics. This study was approved by the University of Pittsburgh Institutional Review Board (IRB number PRO12060174). Individual data on these births was accessed through a password protected application with the PADOH. Information was abstracted regarding maternal risk factors (age, education, cigarette smoking history, use of Women, Infant and Children/WIC assistance, gestational diabetes, prenatal visits, pre-pregnancy weight, and birth parity) as well as gestational age and gender of child at birth [28]. Multiple births, records without a valid geocode (X, Y coordinate), and those with missing birth outcome and demographic information were excluded from the analysis. Exact point distances between singleton-birth residences with complete information and natural gas wells were calculated using ArcMap (version 10.1; ESRI Inc., Redlands, CA).

We calculated an inverse distance weighted (IDW) well count for each mother living within 10-miles of UGD to account for both the number of unconventional wells within this buffer as well as distance of each well from the mother's residence [27]. This metric, shown below in

Eq 1, gives greater weight to unconventional wells closest to the mother's residence:

$$\text{IDW well count} = \sum_{i=1}^{n} \frac{1}{di} \quad (1),$$

where the IDW well count is the inverse distance weighted count of unconventional wells within a 10-mile radius of maternal residence in the birth year, n is the number of existing unconventional wells within a 10-mile radius of maternal residence in the birth year, and d_i is the distance of the i^{th} individual well from the mother's residence. For example, a mother's residence that has two wells, both 0.5 mile away, would have an IDW well count of 4. Mothers were categorized into exposure quartiles according to their IDW well counts:

Group 1: IDW Well Count >0 but <0.87

Group 2: IDW Well Count ≥0.87 but <2.60

Group 3: IDW Well Count ≥2.60 but <6.00

Group 4: IDW Well Count ≥6.00

Three indicator variables were created, using the first quartile (Group 1) as the referent group. The 10% of births that did not live within 10 miles of UGD were eliminated from the analysis due to notable sociodemographic differences; these mothers were more African American (7% compared to 3%), smoked more during pregnancy (25% versus 20%), and had a higher proportion receiving WIC assistance (41% versus 32%).

The outcomes assessed were continuous birth weight, small for gestational age (SGA), and prematurity (gestational age <37 weeks). To identify SGA births, birth weights were normalized to gestational age and estimates of SGA were deduced from nomograms identifying elements of fetal growth (SGA <10% of predicted weight for a given gestational age and gender) [29]. Mean birth weights in each group were compared using analysis of variance (ANOVA), and proportions of SGA and premature infants were compared using chi-square tests. Outcomes were modeled using multivariate linear regression (continuous birth weight) or logistic regression (SGA and prematurity). All models were adjusted for gender of the child and mother's age, education (8^{th} grade or less; 9^{th}-12^{th} grade, no diploma; high school graduate or GED completed; some college credit, but not a degree; associate degree; bachelor's degree; master's degree; doctorate or professional degree), pre-pregnancy weight, prenatal care (1 if at least 1 visit; 0 otherwise), smoking (1 if smoked at all during pregnancy; 0 otherwise), gestational diabetes (1 if present; 0 otherwise), WIC (1 if received; 0 otherwise); African American (1 if yes; 0 otherwise) and parity (first child; second child; third child; fourth child or greater). The model for continuous birth weight was also adjusted for gestational age to account for the downward shift in birth weights accompanying shorter gestational ages due to earlier obstetric intervention observed in our dataset from the PADOH as well as nationally [30]. All statistical tests were performed using IBM SPSS Statistics 21 and assessed at a significance level of $\alpha = 0.05$.

Results

Descriptive statistics

This analysis included 509 active unconventional natural gas wells in Butler, Washington and Westmoreland counties from 2007 to 2010, representing 18% of the state-wide total of 2,864 [2]. Fig 1 shows the steps used to eliminate unavailable and missing birth certificate data, leading to the final sample of births with complete information. There were 28,999 total births in these three counties from 2007 to 2010, and 27,997 (97%) of these were singleton live births. Out of the singleton birth residences, 5,724 (20%) were not geocoded to an X,Y coordinate and,

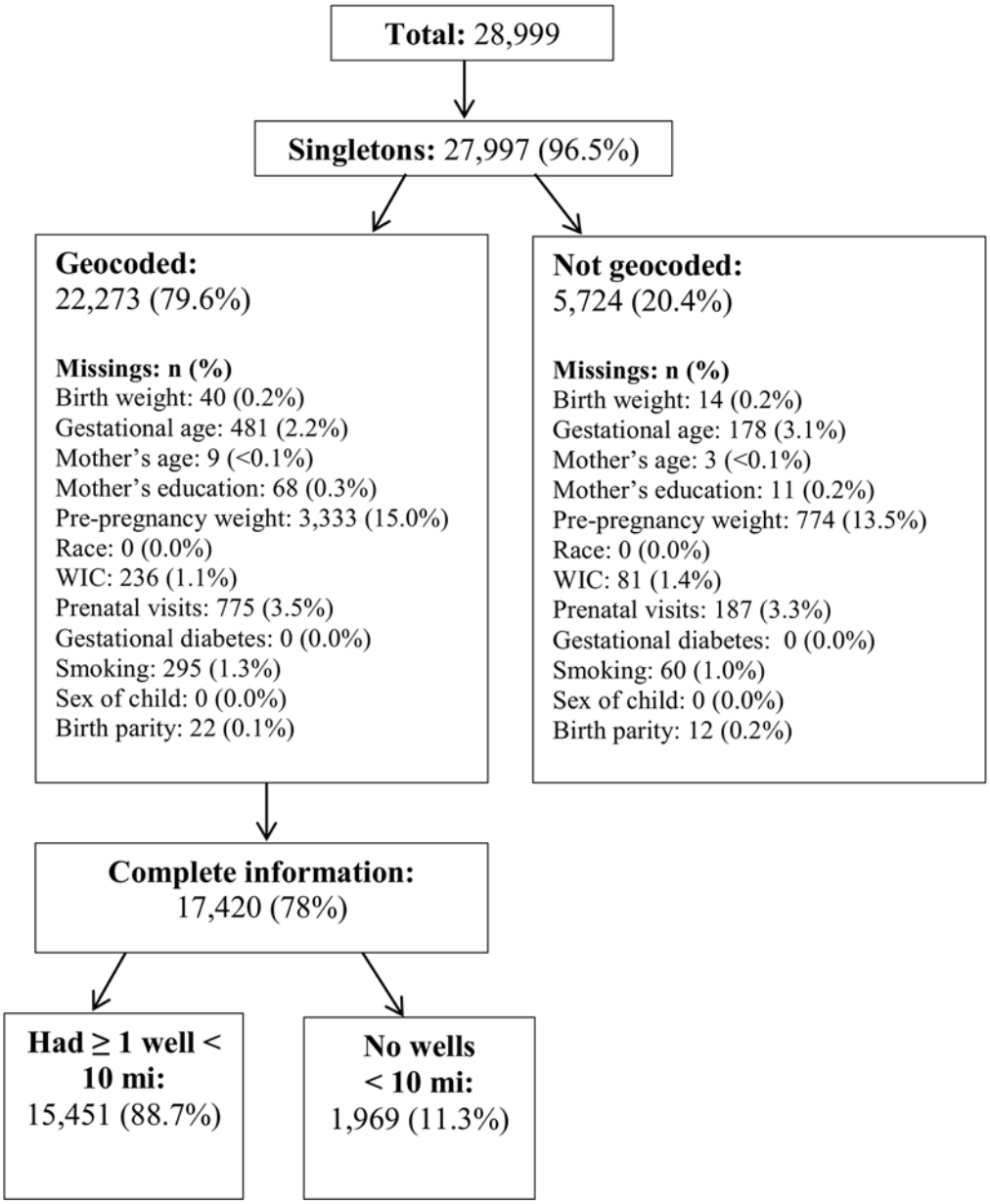


Fig 1. Flowchart of sample sizes and missing data for births in Butler, Washington, and Westmoreland Counties 2007–2010.

doi:10.1371/journal.pone.0126425.g001

since the dataset did not include an address or zip code for the mother's residence, were excluded from the analysis. This left 22,273 singleton births available for further analysis in ArcGIS. Birth weight was missing for 0.2% of these geocoded singleton births, and gestational age was missing for 2.2%. Mother's age, mother's education, and birth order were missing for less than 1% of births. Pre-pregnancy weight was missing for 15% of mothers, WIC assistance for 1.1%, the number of prenatal visits for 3.5%, and information on smoking for 1.4%. The remaining 17,420 births had complete geographical and birth certificate information. Of these, 15,451 (89%) had at least one well within 10-miles of the mothers residence.

Table 1. Maternal and Child Risk Factors.

Factor	Total N = 15,451	Referent (First Quartile)[a] N = 3,604	Second Quartile[a] N = 3,905	Third Quartile[a] N = 3,791	Fourth Quartile[a] N = 4,151
Mother's age (years)[b]	28.6 ± 5.8	28.8 ± 5.8	28.7 ± 5.8	28.6 ± 5.7	28.3 ± 5.8
Mother's Education (% high school graduate/GED) [b]	22.7%	22.1%	22.5%	22.6%	23.6%
Pre-Pregnancy Weight (lbs) [b]	153.8 ± 39.1	152.6 ± 38.2	152.9 ± 38.2	155.2 ± 40.2	154.7 ± 39.9
Race (% African American) [b]	3.0%	2.6%	2.0%	3.4%	4.1%
WIC (% assistance) [b]	32.1%	29.6%	31.0%	33.6%	34.1%
Prenatal care (% at least one visit)	99.5%	99.5%	99.5%	99.5%	99.3%
Presence of gestational diabetes	4.1%	4.7%	3.7%	4.3%	3.9%
Cigarette smoking during pregnancy[b]	20.0%	19.6%	18.8%	19.9%	21.7%
Gestational age (weeks) [b]	38.7 ± 1.9	38.6 ± 1.9	38.8 ± 1.8	38.7 ± 1.9	38.7 ± 1.9
Birth weight (g) [b]	3345.8 ± 549.2	3343.9 ± 543.9	3370.4 ± 540.5	3345.4 ± 553.5	3323.1 ± 558.2
Small for gestational age[b]	5.5%	4.8%	5.2%	5.6%	6.5%
Premature[b]	7.7%	8.0%	6.7%	8.4%	7.9%
Congenital anomalies[b]	0.5%	0.3%	0.7%	0.4%	0.5%
Percent female	48.5%	48.7%	48.3%	48.6%	48.5%
Birth parity (first)	42.7%	42.8%	41.7%	42.2%	44.1%

[a]Referent (First quartile), <0.87 wells per mile; Second quartile, 0.87 to 2.59 wells per mile; Third quartile, 2.60 to 5.99 wells per mile; Fourth quartile, ≥6.00 wells per mile.

[b]Difference between quartiles is significant (p<0.05).

doi:10.1371/journal.pone.0126425.t001

Table 1 shows the demographics of these 15,451 infant-mother pairs by quartile (the referent group (first quartile) and three exposure quartiles) as well as the proportions of SGA and premature infants in each group. Mother's education and parity were categorized into 8 and 4 groups, respectively; results are presented for percentage that completed high school/GED and first child. There were no significant differences in prenatal care, gestational diabetes, child gender, or parity between the referent and exposure quartiles. Differences in gestational ages and mother's ages between the four groups were small but statistically significant. Mother's education, pre-pregnancy weight, race, WIC assistance, and smoking were also statistically different between the four groups. Chi-square analyses showed statistically significant differences in the proportions of SGA and preterm births. All proportions of SGA were significantly less than the 10% expected for the population [31] but were similar to the general population (regardless of proximity to well) in various counties in our study.

Model Results

Table 2 shows the multivariate linear regression results for birth weight, adjusted for mother's age, education, pre-pregnancy weight, gestational age, child gender, prenatal visits, smoking, gestational diabetes, WIC, race, and birth order. After accounting for these factors, we found that infants in the highest (fourth) exposure quartile tended to have lower birth weights than those in the referent group (p = 0.02). There were no significant differences in birth weight between the other exposure quartiles and the referent group. In accord with our current understanding [32], higher birth weights were associated with mothers that were younger, more educated, had higher pre-pregnancy weights, had more prenatal care, did not smoke during pregnancy, had gestational diabetes, did not receive WIC, were Caucasian, and had previous

Table 2. Multivariate Linear Regression of Birth Weight and Proximity.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Significance (P)
	B	*Standard Error*	*Beta*		
Constant	-3711.86	93.06	-39.88		<0.01
Mother's Age	-2.95	0.77	-0.03	-3.82	<0.01
Mother's Education	17.88	2.72	0.05	6.58	<0.01
Pre-Pregnancy Weight	2.01	0.09	0.15	23.37	<0.01
Gestational Age	172.64	1.97	0.56	87.51	<0.01
Female	-133.90	6.63	-0.12	-20.19	<0.01
Prenatal Care	127.07	51.53	0.02	2.47	0.01
Smoking During Pregnancy	-184.69	9.07	-0.14	-20.37	<0.01
Gestational Diabetes	33.57	16.82	0.01	2.00	0.05
WIC	-27.44	8.62	-0.02	-3.18	<0.01
Race	-146.22	19.88	-0.05	-7.36	<0.01
Birth parity	65.89	4.01	0.12	16.41	<0.01
Low[a]	10.55	9.52	0.01	1.11	0.27
Medium[a]	-0.48	9.59	0.00	-0.05	0.96
High[a]	-21.83	9.39	-0.02	-2.32	0.02

[a]Low, Second quartile to referent; Medium, Third quartile to referent; High, Fourth quartile to referent.

doi:10.1371/journal.pone.0126425.t002

children. Higher birth weights were also associated with longer gestational ages and being male.

Fig 2 shows the unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for SGA. The steady increase in SGA across quartiles (Table 1) resulted in a progressive increase in odds ratios for SGA (unadjusted or adjusted), suggestive of a dose-response relationship. In the adjusted model, the highest exposure group compared to the referent reached significance (OR = 1.34, 95% CI = 1.10–1.63).

Fig 3 shows the unadjusted and adjusted odds ratios and 95% confidence intervals for prematurity. Prematurity was associated with mothers that were older, less educated, had no prenatal care, smoked, had gestational diabetes and had no previous births. Male babies were also more likely to be premature than females. There was no significant effect of well density on prematurity except for a slightly lower proportion of premature infants born to mothers in the second exposure quartile compared to the referent (adjusted OR = 0.82, 95% CI = 0.68–0.98).

Discussion

We accessed public records of UGD and birth and used a geographic information system that enabled proximity and density of nearby UGD to be used as a surrogate for exposure. Based on this latter estimate, we identified four groups of mothers of comparable size that gave birth in the study period (2007–2010) in three counties in Southwest Pennsylvania with high levels of UGD activities. These four groups were relatively similar in various determinants of maternal and child risks for perinatal outcomes but had different levels of exposure (i.e. IDW well count) (Table 1). The information was readily compatible for multivariate linear and logistic regression analysis in which covariates of risk could be accounted for (at least within limits of available birth certificate data in Pennsylvania) and contribution of exposure could be assessed. Even when the SGA births were removed, a small but significant decrement in mean birth weight by quartile of exposure remained ($p<0.05$). McKenzie et al. were able to explore subsets

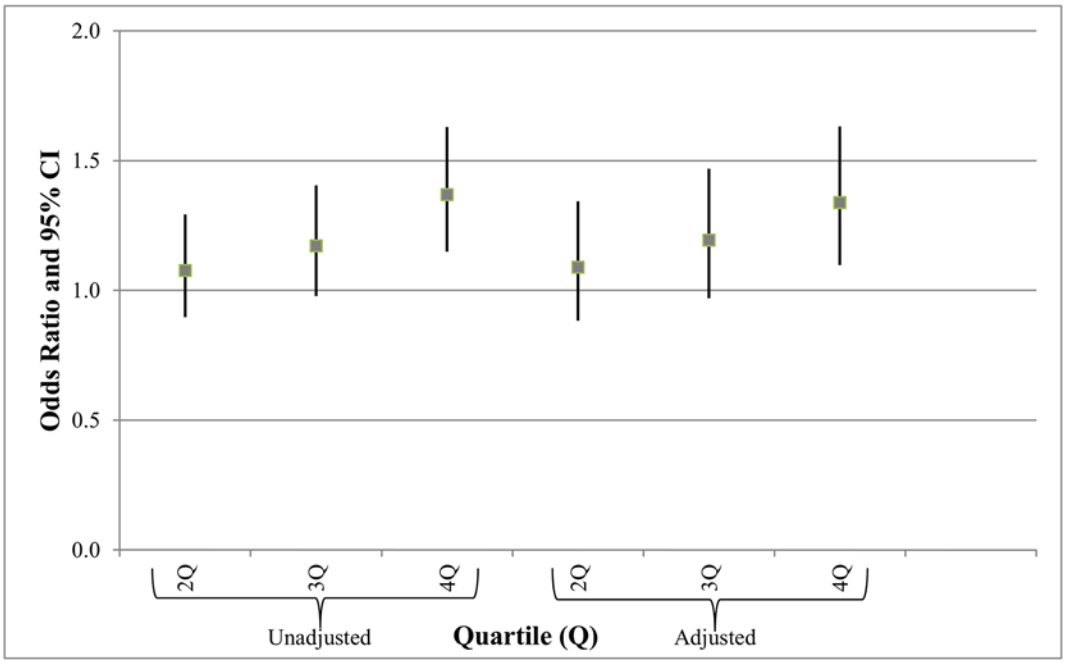


Fig 2. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for small for gestational age (adjusted for mom's age, mom's education, pre-pregnancy weight, gender of infant, prenatal visits, smoking during pregnancy, gestational diabetes, WIC, race, and birth order). Key: Referent (First quartile), <0.87 wells per mile; Second quartile (2Q), 0.87 to 2.59 wells per mile; Third quartile (3Q), 2.60 to 5.99 wells per mile; Fourth quartile (4Q), ≥6.00 wells per mile.

doi:10.1371/journal.pone.0126425.g002

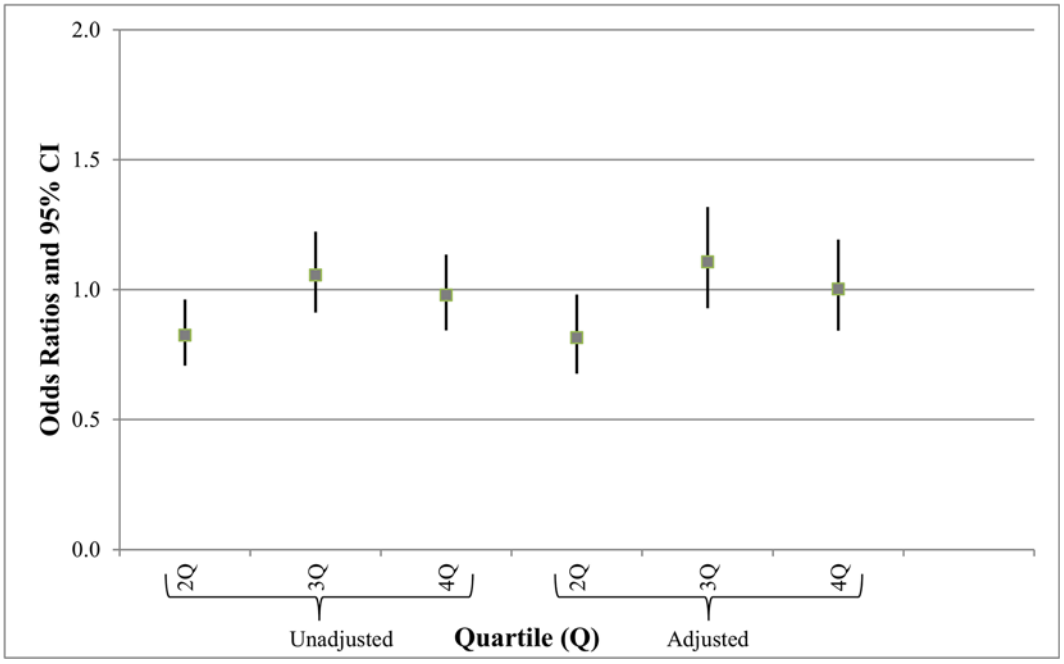


Fig 3. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for prematurity (adjusted for mom's age, mom's education, pre-pregnancy weight, gender of infant, prenatal visits, smoking during pregnancy, gestational diabetes, WIC, race, and birth order). Key: Referent (First quartile), <0.87 wells per mile; Second quartile (2Q), 0.87 to 2.59 wells per mile; Third quartile (3Q), 2.60 to 5.99 wells per mile; Fourth quartile (4Q), ≥6.00 wells per mile.

doi:10.1371/journal.pone.0126425.g003

of congenital anomalies and neural tube defects [27], but our dataset had insufficient power to explore such birth defects.

Comparison of existing studies on UGD and perinatal outcomes

This analysis adds to possible health impact concerns recently described by McKenzie et al. in which there was an increase in birth defects associated with proximity to UGD in rural Colorado [27]. In contrast to the McKenzie et al. study [27], our observation of a decrement in birth weight in the highest exposure group is similar to preliminary reports of two other studies, including the original thesis work of Elaine Hill [33] and a recent abstract [34]. The differences in these studies on effects of UGD on birth weight from Colorado (where proximity and density were associated with a protective effect) underscore the importance of assessing health impacts in a region-specific fashion.

Geological differences are known to account for differences in flowback water composition in different shale gas areas [35]. A notable regional difference between Colorado and Pennsylvania is that the disposal of flowback fluids is far more likely to lead to human exposure in Pennsylvania where deep underground injection has not been feasible [6]. Surface disposal sites are not readily available for geolocating, and thus could not be used in our IDW model. However, impoundments and other sites to which the flowback water is piped or trucked are likely to be near drilling sites, particularly when there are multiple sites in the area, and impoundments have been demonstrated to leak [6, 8]. Therefore, the IDW model is still likely to be representative of exposure risk. There are also important regional differences within Pennsylvania that may be pertinent to a comparison of our findings with those of other studies. Southwestern Pennsylvania is a "wet gas" area, which contains far higher levels of benzene and other relatively higher weight shale gas components than do the "dry gas" areas of the rest of the Marcellus Shale regions of the state. The management of flowback fluids presents a risk of air pollution as well as water pollution. Studies with cooperating industries have shown very wide variation from site to site in methane emissions, and in worker benzene exposures [11, 36].

McKenzie et al. [27] established criteria to restrict their analysis to rural areas, thereby minimizing the contributions of other industries, traffic, congestion and other confounding influences of a more urban environment. Although UGD in Southwestern PA does not include the most dense areas of Allegheny County, the population density in the counties we studied surrounding Pittsburgh are greater than rural Colorado [37]; thus, our assessment of exposure likely included different contributing sources of confounding pollution and other variables. McKenzie et al. [27] also included impact of altitude that is important in Colorado but can be overlooked in the comparatively modest elevations in Southwestern PA. Non-white mothers were excluded in their analysis (as it was too small a group within existing cohorts) and their referent group was individuals >10 miles from UGD [27]. This group of mothers (those >10 miles) in the present study was composed of a somewhat different demographic of women than those living within 10 miles of UGD and were therefore excluded from the analysis; most notably, these mothers were more African American (7% compared to 3%), smoked more during pregnancy (25% versus 20%), and had a higher proportion receiving WIC assistance (41% versus 32%) (see Table 3). In our study, 20% of mothers reported smoking during pregnancy (see Table 1) and, although slightly higher than the overall prevalence for the state of Pennsylvania (15%), it is similar to other reports of smoking during pregnancy for the counties and the time period under study [38]. According to the Pennsylvania Department of Health, the percent of mothers that smoked during pregnancy from 2010 to 2012 was 15% in Butler, 22% in Washington, and 20% in Westmoreland [38]. In a random sample of 5,007 birth certificates

Table 3. Maternal and Child Risk Factors for Geocoded versus Not Geocoded Residences and Those With versus Without at Least One Well Within 10-miles.

Factor	Geocoded N = 22,273	Not geocoded N = 5,724	<10-miles N = 15,451	≥10-miles N = 1,969
Mother's age (years)	28.5 ± 5.8	28.1 ± 6.0	28.6 ± 5.8	27.5 ± 5.9
Mother's Education (% high school graduate/GED)	23.3%	25.6%	22.7%	27.4%
Pre-Pregnancy Weight (lbs)	154.1 ± 39.4	153.6 ± 39.4	153.8 ± 39.1	156.5 ± 41.9
Race (% African American)	3.5%	3.4%	3.0%	7.2%
WIC (% assistance)	33.2%	36.1%	32.1%	41.3%
Prenatal care (% at least one visit)	99.4%	99.1%	99.5%	99.4%
Presence of gestational diabetes	4.2%	4.4%	4.1%	4.4%
Cigarette smoking during pregnancy	20.9%	22.1%	20.0%	25.7%
Gestational age (weeks)	38.7 ± 1.9	38.7 ± 2.0	38.7 ± 1.9	38.5 ± 2.2
Birth weight (g)	3343.0 ± 553.9	3333.6 ± 558.9	3345.8 ± 549.2	3319.8 ± 594.8
Percent female	48.5%	50.0%	48.5%	48.5%
Birth parity (first)	42.6%	43.2%	42.7%	42.0%

doi:10.1371/journal.pone.0126425.t003

from 2005 to 2009 we obtained from the PADOH for a separate study, the proportions of mothers that smoked prior to and during pregnancy were also higher than the state: 20% for Butler, 32% for Washington, and 29% for Westmoreland.

Like McKenzie et al. [27], we were persuaded that previous experience with multiple fixed sources of pollution and birth outcomes suggests that inverse density is the best surrogate for maternal exposure [39–40]. Further, when we repeated the analyses using IDW well count as a continuous measure, the associations between increased exposure and smaller birth weights and increased odds of SGA (OR = 1.009, 95% CI = 1.003–1.015) remained significant ($p<0.01$). A sensitivity analysis of 2010, the year with the most UGD activity in our study period, also showed an association between increased exposure and decreasing birth weights ($p = 0.03$). A reanalysis (data not shown) adding county (categorically) to the adjusted linear regression led to similar conclusions regarding: a) association of lower birth weight and increased well density for the fourth quartile ($p = 0.02$); and b) increased odds of SGA for the highest exposure group (OR = 1.34, 95% CI = 1.10–1.63, $p = 0.004$).

Two other concomitant studies have findings similar to ours concerning birth weight. The PhD thesis of Elaine Hill at Cornell University compared birth outcomes for mothers who resided in regions in Pennsylvania in proximity to wells as a function of time (before and after permit and SPUD) [33]. Their model employed a difference-in-differences approach to compare groups that lived near permitted wells versus groups near permitted wells that underwent further development. An increase in prevalence of low birth weight at gestation and reduced 5 minute APGAR scores was reported while no impact on premature birth was detected for offspring of mothers living 1.5 miles or less from gas development [33]. In an abstract presented at a recent Annual Meeting of the American Economic Association, Currie et al. noted that proximity (within 1.5 miles) to a well increased low birth weight at term as measured in a multi-state sample [34]. Our study is the only one that is specifically limited to counties with intensive shale gas activities in Southwestern PA, thereby minimizing the heterogeneity of demography, geology, climate and other confounding variables.

It is only in recent years that drilling technology has rapidly advanced to be able to obtain substantial levels of natural gas tightly bound to deep underground shale layers. This continually evolving technology greatly differs from the past in using perhaps 5 million, rather than 50,000 gallons of hydrofracturing fluid under much higher pressures for each well; in having an evolving suite of hydrofracturing chemicals, with over 500 having been used; in laterally

bending the well within the shale layers for greater than a kilometer; in drilling in multiple directions from the same well head from larger drill pads for sequential periods of six months or longer; and in many other technological advances. Recent reviews of shale gas issues in the United States, Canada and Europe have been consistent in commenting on the lack of health-related information [1, 4].

Limitations

This investigation is semi-ecological in nature. We had individual data on birth outcomes and risk factors; however, the final analysis grouped mothers into exposure categories to provide a clearer picture of possible dose-response relationships. In addition, there may be a number of unknown factors that led to our conclusion that well density was associated with lower birth weight and greater odds of SGA. As in any epidemiological study, these associations do not imply causation and are hypothesis generating only. The observed associations could be due to a contaminant related to UGD, an unknown confounding factor we were unable to account for in our analyses, or chance. Moreover, we assumed that the residence on the birth certificate was synonymous with exposure during the entire pregnancy, as we have no ability to evaluate transient occupancy of the pregnant mother. However, the counties under study have relatively stable populations. US Census data (2008–2012) for living in the same house one year and over for Butler, Washington and Westmoreland Counties shows 88.6%, 88.1% and 91.0% respectively as compared to 84.8% for the US and 87.8% for Pennsylvania [37].

Proximity is a primitive surrogate for exposure itself and is uninformative of route (water, air) or etiologic agent. Our observations were based on data deduced from the Department of Environmental Protection (DEP) of Pennsylvania and assignments of longitude and latitude only from birth certificate data. Twenty percent of the birth certificate records did not have a corresponding geocode and, since no further information on address or zip code was available, these births were excluded from the analysis. However, the sociodemographic characteristics of this group were similar to those that were geocoded (Table 3). Up until recently, pertinent information from DEP was limited to date of permit request and drilling (SPUD) and status (active, plugged or abandoned). The available well permit number provides information on production and waste data [2]. Longitude and latitude defined proximity in our analyses, and we did not probe more complex issues of geology, climate or meteorological conditions; thus, the transmigration of potential pollutants in water or air remains unclear.

Other limitations in the birth dataset included the lack of a birth month and day; we were therefore only able to identify those wells drilled during the birth year of the infant. Active drilling of a well occurs over a period of only a few months, so incorporating more specific timings of exposure will be critical in future work as further data become available as to the time period during which air or water exposures are most likely. Birth weight data are reasonably precise as derived from birth certificates, but such certificates appear less reliable for gestational age [41], so derived information such as SGA may be spuriously affected. We also relied on birth certificates to incorporate non-exposure relative risks for mother and child. Although it is encouraging that in multivariate analyses, many of these contributing factors affected outcomes in a predictable fashion [32], incomplete information on many of these factors may have affected our conclusions in Table 2 and Figs 2 and 3. For example, socioeconomic status was inferred by use of assistance via WIC; smoking was neither quantitatively assessed nor confirmed beyond self-reporting; the details of prenatal care, co-morbidities and nutritional status are not on birth certificates. As such, larger studies that include medical records will be helpful.

The relative monotonic increase in SGA (Table 1) and odds ratios for SGA (Fig 2) lends credence to the possibility that this association is indeed related to increased exposure to aspects

of UGD. Similarly, a significant decrease in birth weight, after adjusting for covariates, was discernable only in the highest exposure quartile (Table 2). In contrast, changes in odds ratios for prematurity were not significant, except for a very small protective effect in the second quartile (Fig 3).

If the association of lower birth weight and proximity to well is indeed secondary to environmental exposure, then identifying the route of exposure and the agents, alone or in combination, is a critical and challenging next step. In the preliminary study of Currie et al. [34], no differences between mothers with access to public or well water was found, suggesting that exposures may not be water derived. Air pollution is well known to affect perinatal outcomes [13, 23–24, 42], and a meta-analysis of 62 studies recently pointed to particulate matter, carbon monoxide and nitrogen dioxide [43]. Potential UGD derived air pollutants that are known to be associated with low birth weight include diesel exhaust [43], heavy metals [21–22, 44], benzene [45] and other volatile organic compounds [46].

In conclusion, a small but significant association between proximity to UGD and decreased birth weight was noted after accounting for a large number of contributing factors available from birth certificate data in Southwest Pennsylvania. Although the medical and public health significance of this is unclear, it was noteworthy that there was a significant increase in incidence of SGA in the most exposed group. Along with the first published study on the association of increased incidence of birth defects and proximity and density of nearby wells in Colorado [27], there is a clear need for more complete studies including larger populations, better estimates of exposure and covariates and more refined medical records. The difference in outcomes as they relate to birth weight between our study and Colorado (but similar findings to ours in the original work of Hill [33] and preliminary results of Currie et al. [34]) underscores the importance of region-specific assessment of UGD impacts on public health. Although neither the route (water, air or soil) of exposure nor etiologic agents could be addressed, this study is among the first to report a human health effect associated with hydrofracturing. The embryo/fetus is particularly sensitive to the effects of environmental agents, which can have significant lifetime consequences [18]; therefore, further investigation appears warranted.

Acknowledgments

The authors would like to thank Dr. Vincent Arena in the Department of Biostatistics at the University of Pittsburgh Graduate School of Public Health for his helpful expertise regarding potential confounding.

Author Contributions

Conceived and designed the experiments: LLB SLS. Performed the experiments: SLS LLB. Analyzed the data: SLS LLB JCL YS BDG BRP EOT. Contributed reagents/materials/analysis tools: SLS LLB JCL YS BDG BRP EOT. Wrote the paper: SLS LLB JCL YS BDG BRP EOT.

References

1. Department of Energy. Modern Shale Gas Development in the United States: A Primer. Washington, DC: US Department of Energy; 2009. Available: http://energy.gov/fe/downloads/modern-shale-gas-development-united-states-primer.
2. Pennsylvania Department of Environmental Protection. Oil and Gas Reports. Available: http://www.portal.state.pa.us/portal/server.pt/community/oil_and_gas_reports/20297. Accessed 15 December 2014.

3. Small MJ, Stern PC, Bomberg E, Christopherson SM, Goldstein BD, Israel AL, et al. Risks and risk governance in unconventional shale gas development. Environ Sci Technol. 2014; 48: 8289–8297. doi: 10.1021/es502111u PMID: 24983403
4. Council Canadian Academics. Environmental impacts of shale gas extraction in Canada; 2014. Available: http://www.assembly.gov.nt.ca/sites/default/files/td_105-175.pdf. Accessed 18 September 2014.
5. Goldstein BD, Brook BW, Cohen SD, Gates AE, Honeycutt ME, Morris JB, et al. The role of toxicological science in meeting the challenges and opportunities of hydraulic fracturing. Toxicol Sci. 2014; 139 (2): 271–283. doi: 10.1093/toxsci/kfu061 PMID: 24706166
6. Adgate JL, Godstein BD, McKenzie LM. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol. 2014; 48: 8307–8320. doi: 10.1021/es404621d PMID: 24564405
7. States S, Cyprych G, Stoner M, Wydra F, Kuchta J, Monnell J, et al. Marcellus Shale drilling and brominated THMs in Pittsburgh, Pa., drinking water. Journal-American Water Works Association. 2013; 105 (8): E432–E448. http://dx.doi.org/10.5942/jawwa.2013.105.0093
8. Wilson JM, VanBriesen JM. Oil and gas produced water management and surface drinking water sources in Pennsylvania. Environmental Practice. 2012; 14(4): 288–300.
9. Ferrar KJ, Michanowicz DR, Christen CL, Mulcahy N, Malone SL, Sharma RK. Assessment of effluent contaminants from three facilities discharging Marcellus Shale wastewater to surface waters in Pennsylvania. Environ Sci Technol. 2013; 47: 3472–3481. doi: 10.1021/es301411q PMID: 23458378
10. Esswein EJ. NIOSH field effort to assess chemical exposures in oil and gas workers: Health hazards in hydraulic fracturing. Washington, DC: The National Academies Press. Preprint. Available: http://www.ohioeha.org/media/7254/Health-Impact-Assessment-of-Shale-Gas-Extraction.pdf#page=42. Accessed 30 March 2015.
11. Lupo PJ, Symanski E, Waller DK, Chan W, Langlois PH, Canfield MA, et al. Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas. Environmental Health Perspectives. 2011; 119(3): 397–402. doi: 10.1289/ehp.1002212 PMID: 20923742
12. Vidic RD, Brantley SL, Vandenbossche JM, Yoxtheimer D, Abad JD. Impact of shale gas development on regional water quality. Science. 2013; 340(6134). doi: 10.1126/science.1235009
13. Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Quality, Atmosphere & Health. 2012; 5(4): 369–381.
14. Entrekin S, Evans-White M, Johnson B, Hagenbuch E. Rapid expansion of natural gas development poses a threat to surface waters. Frontiers in Ecology and the Environment. 2011; 9(9): 503–511.
15. Osborn SG, Vengosh A, Warner NR, Jackson RB. Methane contamination of drinking water accompanying gas well drilling and hydraulic fracturing. Proceedings of the National Academy of Sciences. 2011; 108(20): 8172–8176. doi: 10.1073/pnas.1100682108 PMID: 21555547
16. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Science Total Environment. 2012; 424: 79–87. doi: 10.1016/j.scitotenv.2012.02.018 PMID: 22444058
17. New York State Department of Health. A Public Health Review of High Volume Hydraulic Fracturing for Shale Gas Development. Executive Summary. December 2014. Available: http://www.health.ny.gov/press/reports/docs/high_volume_hydraulic_fracturing.pdf.
18. Sever LE. Epidemiologic Aspects of Environmental Hazards to Reproduction. In: Talbott EO, Craun GF, editors. Introduction to Environmental Epidemiology. Boca Raton: CRC Press, Inc.; 1995; 81–98.
19. Aronson RA, Uttech S, Soref M. The effect of maternal cigarette smoking on low birth weight and preterm birth in Wisconsin, 1991. Wis Med J. 1993; 92(11): 613–617. PMID: 8303897
20. Adriannse HP, Knottnerus JA, Delgado LR, Cox HH, Essed GG. Smoking in Dutch pregnant women and birth weight. Patient Educ Couns. 1996; 28(1): 25–30. PMID: 8852204
21. Quansah R, Jaakkola JJK. Paternal and maternal exposure to welding fumes and metal dusts or fumes and adverse pregnancy outcomes. Int Arch Occup Environ Health. 2009. doi: 10.1007/s00420-008-0349-6
22. Li X, Sundquist J, Sundquist K. Parental occupation and risk of small-for-gestational age births: a nationwide epidemiological study in Sweden. Human Reproduction. 2010; 1–7. doi: 10.1093/humrep/deq004
23. Xu X, Sharma RK, Talbott EO, Zborowski JV, Rager J, Arena VC, Volz CD. PM_{10} air pollution exposure during pregnancy and term low birth weight in Allegheny County, PA, 1994–2000. International Archives of Occupational and Environmental Health. 2011; 84(3): 251–7. doi: 10.1007/s00420-010-0545-z PMID: 20496078

24. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: A multi-country evaluation of effect and heterogeneity. Environmental Health Perspectives. 2013; 121(3): 367–373.

25. Kannan S, Misra DP, Dvonch JT, Krishnakumar A. Exposures to airborne particulate matter and adverse perinatal outcomes: A biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environmental Health Perspectives. 2006; 114(11): 1636–1642. PMID: 17107846

26. Landrigan PJ, Kimmel CA, Correa A, Eskenazi B. Children's health and the environment: public health issues and challenges for risk assessment. Environmental Health Perspectives. 2004; 112: 257–265. PMID: 14754581

27. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environmental Health Perspectives. 2014; Available: http://dx.doi.org/10.1289/ehp.1306722

28. Pennsylvania Department of Health. Birth Statistics: State/County Statistics Birth Weight. Available: http://www.portal.state.pa.us/portal/server.pt?open=514&objID=809799&mode=2. Accessed 18 August 2014.

29. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics. 2010; 125(2): e214–e224. doi: 10.1542/peds.2009-0913 PMID: 20100760

30. Centers for Disease Control and Prevention. Births: Final Data for 2011. National Vital Statistics Reports 2012: Available: http://www.cdc.gov/nchs. Accessed 23 March 2015.

31. Centers for Disease Control and Prevention. Quickstats: Percentage of Small for Gestational Age Births, by Race and Hispanic Ethnicity—United States, 2005. Available: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5750a5.htm. Accessed 30 March 2015.

32. Valero de Bernabé J, Soriano T, Albaladejo R, Juarranz M, Calle ME, Martínez D, Domínguez-Rojas V. Risk factors for low birth weight: a review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2004; 116(1): 3–15. PMID: 15294360

33. Hill EL. Unconventional natural gas development and infant health: evidence from Pennsylvania. Ithaca, NY: Charles Dyson School Applied Economics and Management, Cornell University; 2013. Available: http//:dyson.cornell.edu/research/researchpdf/wp/2012/Cornell-Dyson-wp1212.pdf.

34. Currie J, Deutch J, Greenstone M, Meckel KH. The Impact of the Fracking Boom on Infant Health: Evidence from Detailed Location Data on Wells and Infants [abstract]. American Economic Association Annual Meeting. 2014.

35. Bibby KJ, Brantley SL, Reible DD, Linden KG, Mouser PJ, Gregory KB, et al. Suggested reporting parameters for investigations of wastewater from unconventional shale gas extraction. Environmental Science Technology. 2013; 47(23): 13220–13221. doi: 10.1021/es404960z PMID: 24252069

36. Allen DT, Torres VM, Thomas J, Sullivan DW, Harrison M, Hendler A, et al. Measurements of methane emissions at natural gas production sites in the United States. Proceedings of the National Academy of Sciences. 2013; 110(44): 18023.

37. United States Census Bureau. Map of 2010 population density by county or county equivalent. Available: https://www.census.gov/geo/maps-data/maps/thematic.html. Accessed 18 August 2014.

38. Pennsylvania Department of Health. Epidemiologic Query and Mapping System. Available: https://apps.health.pa.gov/EpiQMS/asp/ChooseDataset.asp. Accessed 19 March 2015.

39. Brauer M, Lencar C, Tamburic L, Kochoorn M, Demers P, Karr C. A cohort study of traffic and air pollution impacts on birth outcomes. Environ Sci Tech. 2008; 116: 680–686.

40. Ghosh JKC, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett M, et al. Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-regression models and measures of air toxics. Am J Epidemiol. 2012; 175: 1262–1274. doi: 10.1093/aje/kwr469 PMID: 22586068

41. DiGiuseppe DL, Aron DC, Ranbom L, Harper DL, Rosenthal GE. Reliability of birth certificate data: a multi-hospital comparison to medical records information. Matern Child Health J. 2002; 6: 169–179. PMID: 12236664

42. Backes CH, Nelin T, Gorr MW, Wold LE. Early life exposure to air pollution: how bad is it? Toxicology Letters. 2013; 216: 47–53. doi: 10.1016/j.toxlet.2012.11.007 PMID: 23164674

43. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environmental Research. 2012; 117: 100–111. doi: 10.1016/j.envres.2012.05.007 PMID: 22726801

44. Shirai S, Suzuki Y, Yoshinaga J, Mizumoto Y. Maternal exposure to low-level heavy metals during pregnancy and birth size. Journal of Environmental Science and Health, *Part A*. 2010; 45(11): 1468–1474. doi: 10.1080/10934529.2010.500942 PMID: 20694885

45. Zahran S, Weiler S, Mielke HW, Pena AA. Maternal benzene exposure and low birth weight risk in the United States: a natural experiment in gasoline reformulation. Environmental Research. 2012; 112: 139–146. doi: 10.1016/j.envres.2011.11.008 PMID: 22177084

46. Forand SP, Lewis-Michl EL, Gomez MI. Adverse birth outcomes and maternal exposure to trichloroethylene and tetrachloroethylene through soil vapor intrusion in New York State. Environmental Health Perspectives. 2012; 129(4): 616–621.

PLOS | ONE

RESEARCH ARTICLE

Unconventional Gas and Oil Drilling Is Associated with Increased Hospital Utilization Rates

Thomas Jemielita[1☯], George L. Gerton[2☯], Matthew Neidell[3], Steven Chillrud[4], Beizhan Yan[4], Martin Stute[4], Marilyn Howarth[2], Pouné Saberi[2], Nicholas Fausti[2], Trevor M. Penning[2], Jason Roy[1], Kathleen J. Propert[1], Reynold A. Panettieri, Jr.[2]*

1 Department of Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States of America, **2** Center of Excellence in Environmental Toxicology (CEET), Airways Biology Initiative, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States of America, **3** Department of Health Policy and Management, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **4** Lamont-Doherty Earth Observatory of Columbia University, Palisades, New York, United States of America

☯ These authors contributed equally to this work.
* rap@mail.med.upenn.edu

Citation: Jemielita T, Gerton GL, Neidell M, Chillrud S, Yan B, Stute M, et al. (2015) Unconventional Gas and Oil Drilling Is Associated with Increased Hospital Utilization Rates. PLoS ONE 10(7): e0131093. doi:10.1371/journal.pone.0131093

Editor: Jaymie Meliker, Stony Brook University, Graduate Program in Public Health, UNITED STATES

Received: February 2, 2015

Accepted: May 28, 2015

Published: July 15, 2015

Data Availability Statement: All relevant data are available in the paper and its Supporting Information files.

Funding: This work was funded by grants from the National Institute of Environmental Health Sciences (www.niehs.nih.gov): P30-ES013508 (GLG MH PS NF TMP JR KJP RAP) and P30-ES009089 (GLG MN SC BY MS MH PS NF TMP JR KJP RAP). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Over the past ten years, unconventional gas and oil drilling (UGOD) has markedly expanded in the United States. Despite substantial increases in well drilling, the health consequences of UGOD toxicant exposure remain unclear. This study examines an association between wells and healthcare use by zip code from 2007 to 2011 in Pennsylvania. Inpatient discharge databases from the Pennsylvania Healthcare Cost Containment Council were correlated with active wells by zip code in three counties in Pennsylvania. For overall inpatient prevalence rates and 25 specific medical categories, the association of inpatient prevalence rates with number of wells per zip code and, separately, with wells per km^2 (separated into quantiles and defined as well density) were estimated using fixed-effects Poisson models. To account for multiple comparisons, a Bonferroni correction with associations of $p<0.00096$ was considered statistically significant. Cardiology inpatient prevalence rates were significantly associated with number of wells per zip code ($p<0.00096$) and wells per km^2 ($p<0.00096$) while neurology inpatient prevalence rates were significantly associated with wells per km^2 ($p<0.00096$). Furthermore, evidence also supported an association between well density and inpatient prevalence rates for the medical categories of dermatology, neurology, oncology, and urology. These data suggest that UGOD wells, which dramatically increased in the past decade, were associated with increased inpatient prevalence rates within specific medical categories in Pennsylvania. Further studies are necessary to address healthcare costs of UGOD and determine whether specific toxicants or combinations are associated with organ-specific responses.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

The United States now leads the world in producing natural gas from shale formations. Shale gas accounted for 40% of all natural gas produced in 2012 [1–4]. In comparison to the early 2000s, natural gas production in the US has increased with more than a 30% increase in production, due in part to the cost-effective combination of horizontal drilling and hydraulic fracturing [1–4].

Unconventional gas and oil drilling (UGOD), including hydraulic fracturing or "fracking", refers to all activities that extract natural gas and oil from rock formations. At distances from 1 to 2 miles below the earth's surface, tight rock formations impede natural gas and oil flow into a drill-hole [3]. Common reservoirs that contain natural gas and oils include: porous sandstones, limestones, dolomite rocks, shale rocks, and coal beds. Hydraulic fracturing and horizontal drilling methods can effectively extract these resources. Typically, after drilling is complete, fissures are formed using a perforating gun; a mixture of water, proppants and hydraulic fracturing chemicals is then pumped into the rock [3,5]. Consequently, the fissures remain open to liberate the gas. These substances as well as contaminants released from the shale are present in the flowback water. Contaminants include naturally occurring radioactive materials [3,4], toxic organics and metals that may enter ground water, contaminating water supplies especially if leakage occurs from casement failure or from holding ponds for waste water [6,7]. Other toxicants and volatile organic compounds, such as benzene, ethylbenzene, toluene and xylene or radionuclides, have been seen in ground waters impacted by UGOD spills [8] or surface waters receiving UGOD-related waste water [9]. The general lack of published baseline (i.e., pre-UGOD) data has limited efforts to associate contamination in drinking water wells to UGOD activities [10]. Additionally, exhaust produced by diesel trucks and off-site diesel engines, as well as emissions from other UGOD activities (e.g., venting, flaring, compressor stations, etc.) may also affect local air quality with potential impact on health [11–13]. Plausibly, increased noise pollution, truck traffic, and psychosocial stress due to community change, which occur due to increased hydro-fracking activity, could impact public health [11].

Despite the growth in hydraulic fracturing, the health consequences of UGOD are unclear [3,4,14,15]. In Pennsylvania (PA), a rise in hydraulic fracturing has raised health concerns, especially since the Marcellus Shale formation underlies two-thirds of Pennsylvania [16]. In northeastern Pennsylvania, most wells were drilled for dry gas rather than gas and oil [17]. We postulate that increases in active or producing wells in Pennsylvania from 2007 to 2011 are associated with increases in inpatient prevalence rates. Three counties, which lie on the Marcellus Shale formation along the northern border of PA, were chosen for this study: Bradford, Susquehanna, and Wayne. Importantly, zip codes in Bradford and Susquehanna Counties significantly increased UGOD over this time period. These counties are some of the greatest producers of natural gas in Pennsylvania, generating 489 million cubic feet of natural gas from 598 wells in 2011 [18]. In contrast, zip codes in Wayne County have no active wells [18]. Specifically, we evaluated the association between inpatient prevalence rates and well density within 25 different medical categories, as well as overall inpatient prevalence rates.

Materials and Methods

This study is an ecological study with the goal of assessing the association between hydro-fracking activity and health care use. Zip code specific inpatient counts were obtained from the time frame of 2007–2011. Only zip codes from the counties Bradford, Susquehanna, and Wayne were considered. For our analysis, only inpatient records for people who resided in one of these three counties were included. Inpatient records of people who came to a hospital in these counties, but did not reside in one of these counties, were excluded. These counties were

of particular interest, since Wayne had no hydro-fracking activity between 2007 and 2011, while Bradford and Susquehanna saw increased hydro-fracking activity. Inpatient counts were then converted into inpatient prevalence rates (details in Statistical Methods). Furthermore, for each zip code, we obtained the number of wells for each year in 2007–2011. In total, there were 67 zip codes considered, with five inpatient prevalence rates/well counts each. Inpatient prevalence rates were the primary outcome of interest with wells as the primary predicator of interest.

Health Utilization Data

Truven Health Analytics (THA) purchased UB92/UB04 inpatient discharge datasets from the Pennsylvania Health Care Cost Containment Council (PHC4). The PHC4 datasets contain all inpatient hospital discharge records, including those for psychiatric and/or behavioral health, rehabilitation, and drug and alcohol treatment, for patients hospitalized in Pennsylvania. Skilled nursing facility (SNF), swing bed, transitional care unit, 23-hour observation, and hospice records are not included. After receipt of state discharge datasets, THA decoded supplied values, checked the validity of information submitted and standardized the format. The ICD-9 diagnosis codes and MSDRGs included in the data pulls can be found in S1 Table, in the supplemental material section.

Truven Health pulled discharge records for patients residing in any of the Bradford, Susquehanna, and Wayne County zip codes for calendar years 2007, 2008, 2009, 2010, and 2011. Treatment records for those patients hospitalized outside of Pennsylvania were not captured. In addition, THA excluded patient records for those patients with dentistry, HIV, and neurosurgery DRGs.

Insurance Coverage Estimates (ICE) Overview

ICE reports by THA showed the total number of people covered by seven different types of insurance by zip code, age group, and sex for every market in the United States. The seven different types of insurance are Medicaid, Medicare, dual eligible, private employer sponsored, private exchanges, private direct, and uninsured. Every person in a zip code who is a resident is assigned an insurance category based on his or her primary insurance coverage. Only non-residents of zip codes were excluded from the analysis.

Demographics Methodology

THA acquires all of its demographic data from The Nielsen Company statistics for every zip code in the United States. Nielsen bases their estimates on products of the United States Census Bureau, including the 2010 Census Summary File 1 (SF1). Details of the methodology and definitions used to create the SF1 data, including field definitions and the 2010 Census questionnaire, are available in the Census 2010 Data Definitions publication [19].

Mapping of Unconventional Gas Wells in Bradford and Susquehanna Counties in Pennsylvania

To create maps of the unconventional gas well locations, the complete data set for 2000–2013 was downloaded as comma separated values (CSV) from the Pennsylvania Department of Environmental Protection Oil and Gas Reporting Website [20] and imported into FileMaker Pro Advanced 13.0.v.3 for further processing. For Fig 1, the data were filtered for unconventional, drilled wells that produced gas in the noted year. We use the state's categorization, such that: "An unconventional gas well is a well that is drilled into an unconventional formation, which is defined as a geologic shale formation below the base of the Elk Sandstone or its

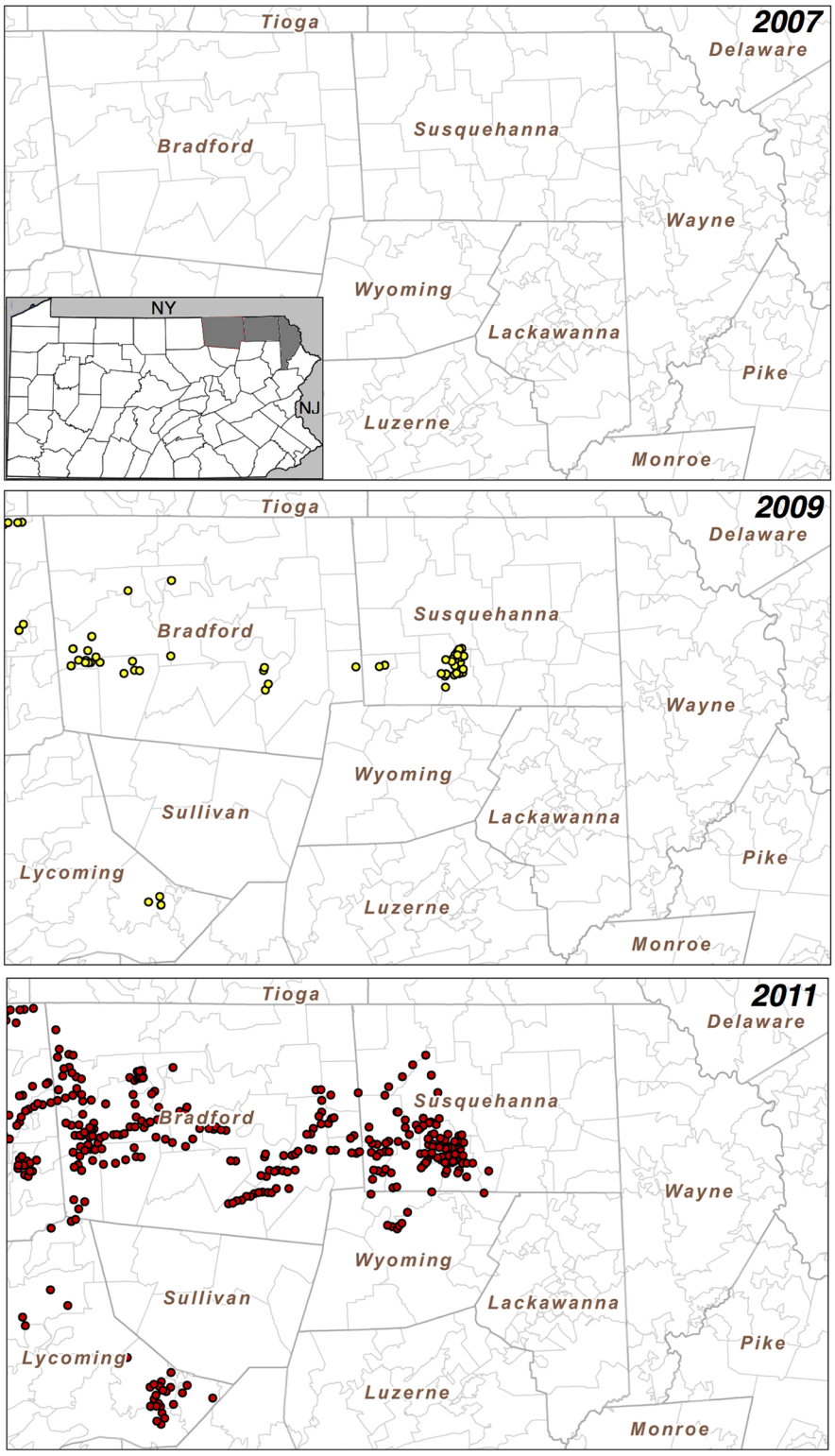


Fig 1. Pennsylvania active wells over time. Pennsylvania active wells in Bradford and Susquehanna Counties increased markedly from 2007 to 2011. Wells are shown as colored dots. From 2007 to 2011, Wayne County effectively had no active wells. Insert in the first panel shows location of Bradford, Susquehanna and Wayne Counties within Pennsylvania.

doi:10.1371/journal.pone.0131093.g001

geologic equivalent where natural gas generally cannot be produced except by horizontal or vertical well bores stimulated by hydraulic fracturing." These data were exported as a DBF file and imported into ESRI ArcGIS v.10.2 to map the locations of the producing wells. In any given year, only wells that produced gas in that year are shown in Fig 1. For example, if a well produced gas in 2007 but did not in 2011, then this well would only appear on the 2007, but not on the 2011 map.

Statistical Analysis

Statistical analysis was performed using STATA 13 software (StataCorp LP, College Station, Texas). Our data included the number of wells and inpatient counts for all combinations of year, medical category (25 total), and zip code within the three chosen counties in PA. In total, after excluding eight zip codes that had no available population information, 67 zip codes were considered. Only inpatient counts for patients that resided in one of three counties were considered. For each zip code, population and total area per square kilometer (km) data were obtained from the US Census 2010. Importantly, zip code specific population and total area per square km were the same for each year in 2007–2011. Number of wells is defined as the number of wells within a specific zip code for a certain year. All data are generated from active wells. We assume that once a well is active in 2007, this same well remains active for the time frame of 2007–2011. For example, if there are 3 wells in 2007 and 8 wells in 2008 for some zip code, then we assume that there were an additional 5 wells created between 2007 and 2008. This is in contrast to the definition of active wells for the mapping, where a well can move from being active to inactive in any given year in 2007–2011. Given the 5-year observation period, very few active wells became inactive. In addition, the actual date of inactivity could not be accurately defined. Furthermore, it is possible that once a well becomes inactive, it could still impact the surrounding community for some period of time. Thus, for the statistical analysis, once an active well enters at any given year, we assume the well remains active for the remainder of the years. In addition to the count of wells, we also generated wells per square km (wells/km^2), which is the number of wells divided by the total area per square km (at the zip code level); we defined this variable as well density. We analyzed both exposure variables (count and density) because, a priori, it was unclear whether the number of wells or the density of wells would have a stronger association with health outcomes. Zip code specific inpatient prevalence rates for each medical category (and overall) were calculated by dividing the zip code specific number of inpatient counts per year by the population of the zip code. The inpatient prevalence rates were then converted into prevalence rates per year per 100 people and treated as the primary outcome for modeling. We now refer to prevalence rates per year per 100 people when we discuss inpatient prevalence rates.

Since we examined a relatively brief interval of time (2007–2011), we postulated that in a given zip code, inpatient prevalence rates would be relatively stable. Our goal was to obtain an un-confounded estimate of the association between inpatient prevalence rates and wells. However, it is possible that observable or unobservable zip code characteristics will be correlated with wells and inpatient prevalence rates. Accordingly, we used conditional fixed effects Poisson regression, where the fixed effects are the zip codes. This controls for all possible characteristics of the zip codes, both measured and unmeasured, that did not change during the period of observation. Thus, if zip codes that consistently have high rates of inpatient prevalence rates are more likely to have more wells over time, this will be accounted for in the model. Alternatively, if there are zip code-level changes from 2007–2011 that affect the number of wells and inpatient prevalence rates, this model will not account for this. Essentially, our methodology captures the association between and within zip code changes in wells and inpatient prevalence

rates. Furthermore, to account for potential over-dispersion, we use robust standard errors [21]. These robust standard errors are cluster-robust estimates, where the clusters are the individual zip codes in this case. Two sets of analyses are then done to investigate the relationship between inpatient prevalence rates and wells.

The first set of analyses relates inpatient prevalence rates to number of wells. Exploratory analyses suggested that the relationship between the log of the inpatient prevalence rates (Poisson model uses a log link) and number of wells was linear. Thus, for these analyses, prediction variables were the number of wells and year (2007–2011). This assumes a linear relationship between number of wells and inpatient prevalence rates, as well as a linear association between inpatient prevalence rates and year. Note that the primary predictor of interest was the number of wells. This will be referred to as the ***number of wells analysis***.

Furthermore, while exploratory analyses suggested a linear relationship between the log of inpatient prevalence rates and number of wells, we also reasoned that a quadratic relationship between the log of inpatient prevalence rates and number of wells was plausible. Subsequently, we also examined whether there exists a non-linear relationship between number of wells and inpatient prevalence rates. Accordingly, a second model incorporated a quadratic relationship between number of wells and inpatient prevalence rates, for each medical category and overall. Prediction variables within this model were year (2007–2011)/wells, and wells^2.

The second set of analyses relates inpatient prevalence rates to wells/km^2 (well density). However, the relationship between inpatient prevalence rates and well density is highly non-linear and heavily influenced by observations that have extremely high wells/km^2. For example, one zip code located in Bradford had 16.9 wells/km^2 and 23.4 wells/km^2 in 2010 and 2011, respectively, while 99% of all wells/km^2 observations had fewer than 4.28 wells/km^2. Subsequently, we opted to separate wells/km^2 into four levels based on quantiles as shown in Table 1. We set Q0wells to be the reference category and all the other levels (Q1wells, Q2wells, Q3wells) to have separate dummy variables. ***This will be referred to as the quantile analysis***.

Our analysis investigates the association of increasing wells/km^2 on inpatient prevalence rates, while allowing for separate associations depending on the magnitude of well/km^2. We, however, recognize that by using quantiles, we lose information and cannot make inference on explicit changes in well density. Furthermore, while our cut-offs are somewhat arbitrary, the goal is to determine whether increased well density is positively associated with inpatient prevalence rates, which is accomplished by this modeling approach. Overall, the primary predictors for this set of analyses included Q1wells, Q2wells, Q3wells, and year. We test the overall Wald test that the coefficients Q1wells = Q2wells = Q3wells = 0.

For all analyses, risk ratios were obtained by taking the exponential of the regression coefficient estimates. Year is recoded into 2007 = 0, 2008 = 1, 2009 = 2, 2010 = 3, and 2011 = 4. We model each medical category separately as well as the overall inpatient prevalence rates, for a total of 26 models per set of analyses. Furthermore, to adjust for multiple comparisons, we use a Bonferroni correction to adjust for testing 25 different medical categories and overall inpatient prevalence rates in both sets of analyses (52 tests). Using an initial level of significance of

Table 1. Definition of quantiles by wells/km^2.

	Q0wells	Q1wells	Q2wells	Q3wells
wells/km^2	0	(0, 0.168]	(0.168, 0.786]	>0.786
Quantile	(0, 65.97]	(65.97, 80]	(80, 90.15]	(90.15, 100]

Note: (A, B] indicates that A is excluded from the range, and B is included.

doi:10.1371/journal.pone.0131093.t001

0.05, this means we reject the null hypothesis that wells are not associated with hospitalizations for $p<0.00096$.

Sensitivity analyses were also performed to determine if removing a specific zip code with much higher inpatient prevalence rates or with much higher well density affected inference. Thus, we removed the specific zip code(s) and recalculated the conditional fixed effects Poisson models, checking to see if the general inference changed.

All of the data obtained for this study were received anonymized and de-identified from Truven Health Analytics. The data were provided as summary information, and there were no unique identifiers. The University of Pennsylvania Committee on the Study of Human Subjects deemed this work non-human subject research.

Results

Subject Demographics by County

The three Pennsylvania counties chosen for analysis were Bradford, Susquehanna, and Wayne. These counties were selected given the completeness of health care utilization data from 2007 to 2011. Bradford and Susquehanna Counties also had large increases in active wells over this time period. Wayne County, which effectively had no active wells from 2007 to 2011, served as a unique control population whose demographics were comparable to Bradford and Susquehanna Counties. The total number of residents as per the most recent census in Bradford, Susquehanna, and Wayne Counties was 157,311. As shown in Table 2, the summary of subject demographics for the three Pennsylvania counties obtained from US census data was comparable. Even though the statistical analysis is done at the zip code level, a county level demographic table is an informative summary of the zip codes that are within the counties. Each county is

Table 2. Characteristics Table for PA Counties.

		Bradford	Susquehanna	Wayne
Population		62,622	43,356	51,548
Overall Hospitalizations 2007–2011		39,821	22,559	30,425
Age (median)		43.4	45.1	45.9
Male %		49.5	50.4	52.8
High School Graduate, percent of person age 25+ %		86.6	88.1	87.4
Bachelor Degree or Higher, percent of person age 25+ %		16.4	16.1	18.4
Median Income (2008–2012) $		44,650	46,815	50,153
Race %	White	97.4	98.0	94.7
	Black	0.6	0.4	3.5
	Asian	0.6	0.3	0.5
	Other	1.4	1.3	1.3
Median Number of Wells	2007	0	0	0
	2008	1	0	0
	2009	13	0	0
	2010	81	1	0
	2011	149	6	0
Number of Zip Codes with >0 Wells (%)	2007	4 (19)	2 (9)	0 (0)
	2008	12 (57)	4 (17)	0 (0)
	2009	16 (76)	8 (35)	0 (0)
	2010	20 (95)	12 (52)	0 (0)
	2011	20 (95)	16 (70)	0 (0)

doi:10.1371/journal.pone.0131093.t002

one data point, so no formal statistical comparison is possible. There were no striking differences among the three counties. The subjects were predominantly Caucasian with few people obtaining higher than a high school diploma. Further, the median income was similar among the counties. Table 2 also illustrates the growth in hydro-fracking activity from 2007 to 2011 for Bradford and Susquehanna. By 2011, 95% of the zip codes in Bradford had at least one well, while 70% of the zip codes in Susquehanna had at least one well.

Inpatient Prevalence Rates by Medical Category

Table 3 shows the median inpatient prevalence rates and median inpatient counts, along with the interquartile range (IQR), for each medical category as well as overall. The median inpatient prevalence rates and median inpatient counts are to be interpreted at the zip code level. Notably, there are a number of categories with very low (or zero) median inpatient prevalence rates and median inpatient counts. Furthermore, cardiology inpatient prevalence rates/inpatient counts seem to be higher than the other medical categories (excluding overall), with a median cardiology inpatient prevalence rate of 1.99 and a median cardiology inpatient count of 18.

Table 3. Median Inpatient Prevalence Rates per 100 people and Median Inpatient Counts, by Medical Category.

Medical Category	Median Inpatient Prevalence Rate (IQR)	Median Inpatient Counts (IQR)
Inpatient total	12.12 (10.05, 14.84)	106 (41, 272)
Cardiology	1.99 (1.42, 2.56)	18 (6, 46)
Dermatology	0.21 (0.09, 0.34)	2 (1, 6)
Endocrine	0.22 (0.01, 0.37)	2 (0.5, 7)
Gastroenterology	1.02 (0.71, 1.43)	10 (3, 27)
General medicine	0.58 (0.32, 0.88)	5 (2, 14)
Generals surgery	0.75 (0.47, 1.01)	6 (3, 19)
Gynecology	0.14 (0, 0.26)	2 (0, 5)
Hematology	0.05 (0, 0.14)	1 (0, 3)
Neonatology	0.12 (0, 0.23)	2 (0, 4)
Nephrology	0.34 (0.18, 0.53)	3 (1, 9)
Neurology	0.58 (0.35, 0.88)	5 (2, 16)
Normal newborns	0.68 (0.41, 0.99)	6 (2, 17)
Ob/delivery	0.84 (0.52, 1.12)	7 (2.5, 21)
Oncology	0.17 (0, 0.29)	2 (0, 6)
Ophthalmology	0 (0, 0)	0 (0, 0)
Orthopedics	1.08 (0.72, 1.42)	10 (4, 26)
Other/ob	0 (0, 0.09)	0 (0, 2)
Otolaryngology	0.08 (0, 0.17)	1 (0, 3)
Psych/drug abuse	0.52 (0.27, 0.85)	5 (2, 16)
Pulmonary	1.18 (0.84, 1.69)	10 (4, 28)
Rheumatology	0 (0, 0.09)	0 (0, 2)
thoracic surgery	0.08 (0, 0.16)	1 (0, 3)
Trauma	0.03 (0, 0.09)	1 (0, 2)
Urology	0.17 (0, 0.27)	2 (0, 5)
Vascular surgery	0.09 (0, 0.19)	1 (0, 3)

Note: Median inpatient prevalence rates/median inpatient counts for each medical category and overall are presented, along with the interquartile range (IQR). Median inpatient prevalence rates/median inpatient counts are interpreted at the zip code level.

doi:10.1371/journal.pone.0131093.t003

Geographic Location of Wells from 2007 to 2011

Given the demand in accessing the Marcellus Shale for UGOD, we next examined the active wells over time. There was a dramatic increase in the number of active wells from 2007 to 2011 as shown in Fig 1. In Bradford and Susquehanna Counties, there were substantial increases in the total numbers of wells with two zip codes having the greatest number of wells with 400 and 395, respectively. In Wayne County, there were no active wells from 2007 to 2011. The most dramatic increases were in Bradford County where wells were acquired more uniformly than those in Susquehanna County, where active wells were primarily located in the southwest corner as shown in Fig 1. Gas production tracked with increasing active well numbers from 2007–2013 as shown in Fig 2. These data suggest that if UGOD continues at the rates observed between 2007 and 2011, well densities are likely to continue to increase. Within the counties, there were also profound differences in wells by zip code. For example, in 2011, 31 zip codes had no wells, but 17 zip codes had at least 100 wells.

Increases in Active Wells Are Associated with Increases in Inpatient Prevalence Rates

Given the rapid increase in wells, we reasoned that increases in wells were associated with changes in inpatient prevalence rates. Of the 67 zip codes examined in the three counties, total inpatient counts from 2007 to 2011 were 92,805. There was marked variation in inpatient prevalence rates across zip codes. Specifically, one zip code had a much higher combined inpatient rate as compared with others as shown in Fig 3. Fig 3 also shows that, within each zip code, the contribution by year was comparable, suggesting that within each zip code, the inpatient rates are relatively stable from 2007–2011 Indeed, the average overall inpatient prevalence rates for 2007–2011 are, respectively, 15.18, 15.30, 14.86, 14.00, 14.25. This indicates that on average, zip code overall inpatient prevalence rates were relatively stable or possibly declining from 2007 to 2011, which mirrors national trends [22]. Fig 4 shows how in 2007, 91% (61/67) of zip codes had no wells. However, by 2011, only 46% (31/67) of zip codes had no wells while 54% of zip codes had least 1 well. Notably, many zip codes had a large number of wells by 2011. 28% (19/67) of zip codes had greater than 0.79 wells/km^2, which equates to 79 wells for every 100 km^2. Importantly, Fig 4 corresponds to the quantile analysis.

To further understand health consequences by disease category, we modeled the 25 top specific medical categories and total inpatients, investigating the association between number of wells and inpatient prevalence rates and the association between well density and inpatient prevalence rates. Only cardiology inpatient prevalence rates were significantly associated with number of wells, taking into account our Bonferroni correction ($p<0.00096$) as shown in Table 4. While other medical categories did not strictly meet the Bonferroni correction boundary, a positive association of well number with inpatient prevalence rates within dermatology, neonatology, neurology, oncology, and urology was also evident. Cardiology and neurology inpatient prevalence rates were also significantly associated with well density as shown in Table 5. Furthermore, these results suggest an almost monotonic increase in the impact of well density on cardiology inpatient prevalence rates, considering how the risk ratio increases moving from quantiles (Q1wells to Q2wells to Q3wells). Evidence also suggests that well density was positively associated within the medical categories of dermatology, endocrine, neurology, oncology, urology, as well as overall inpatient prevalence rates ($p = < 0.05$). Furthermore, for both sets of analyses, the year variable is significantly and negatively associated with inpatient prevalence rates, within the medical categories of gynecology and orthopedics.

In both the number of wells analyses and the well density quantile analyses, cardiology inpatient prevalence rates were significantly associated with wells. Under the quantile analyses,

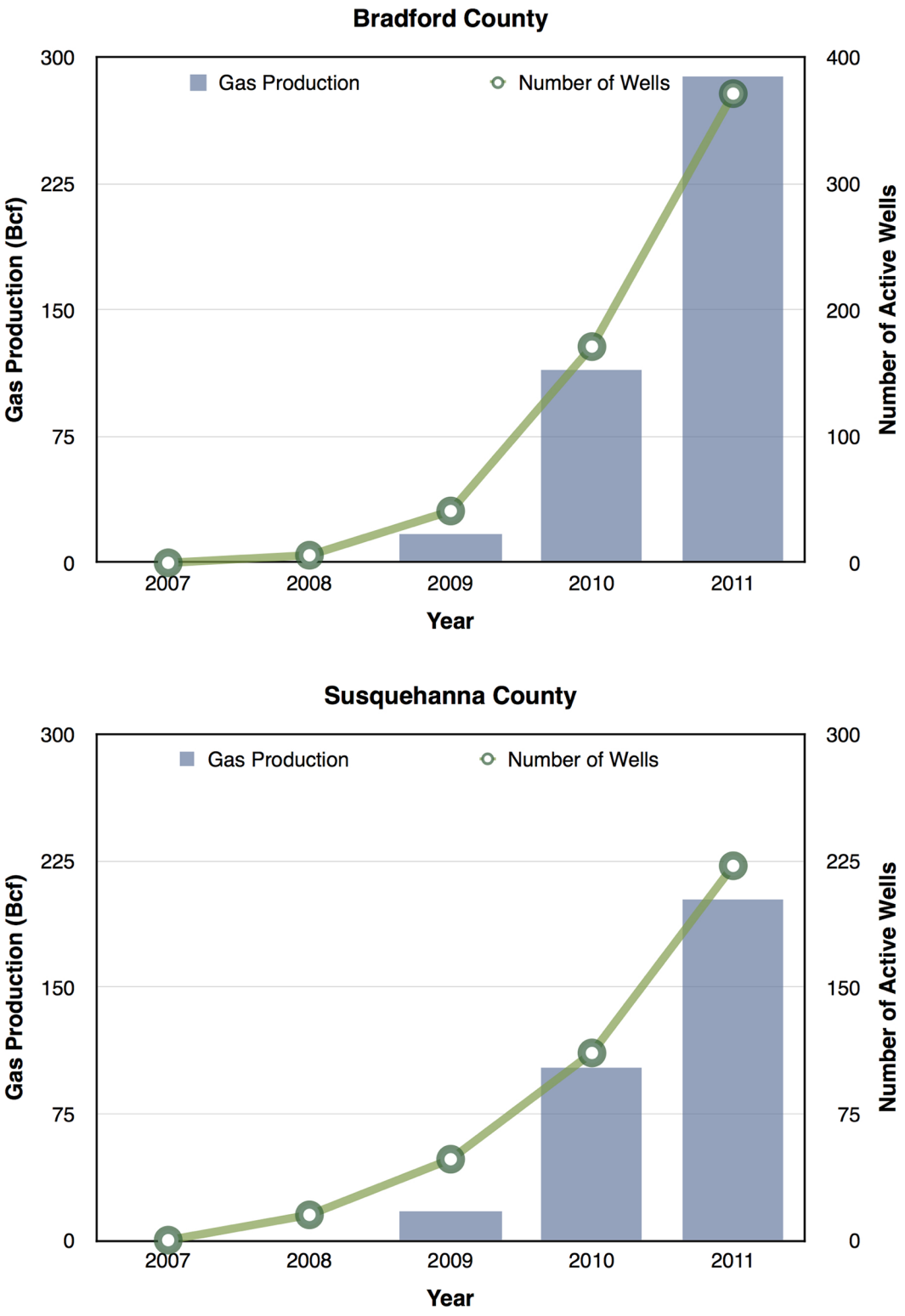


Fig 2. Gas production (histogram) linearly tracked with well number (open circles) from 2007–2011.

doi:10.1371/journal.pone.0131093.g002

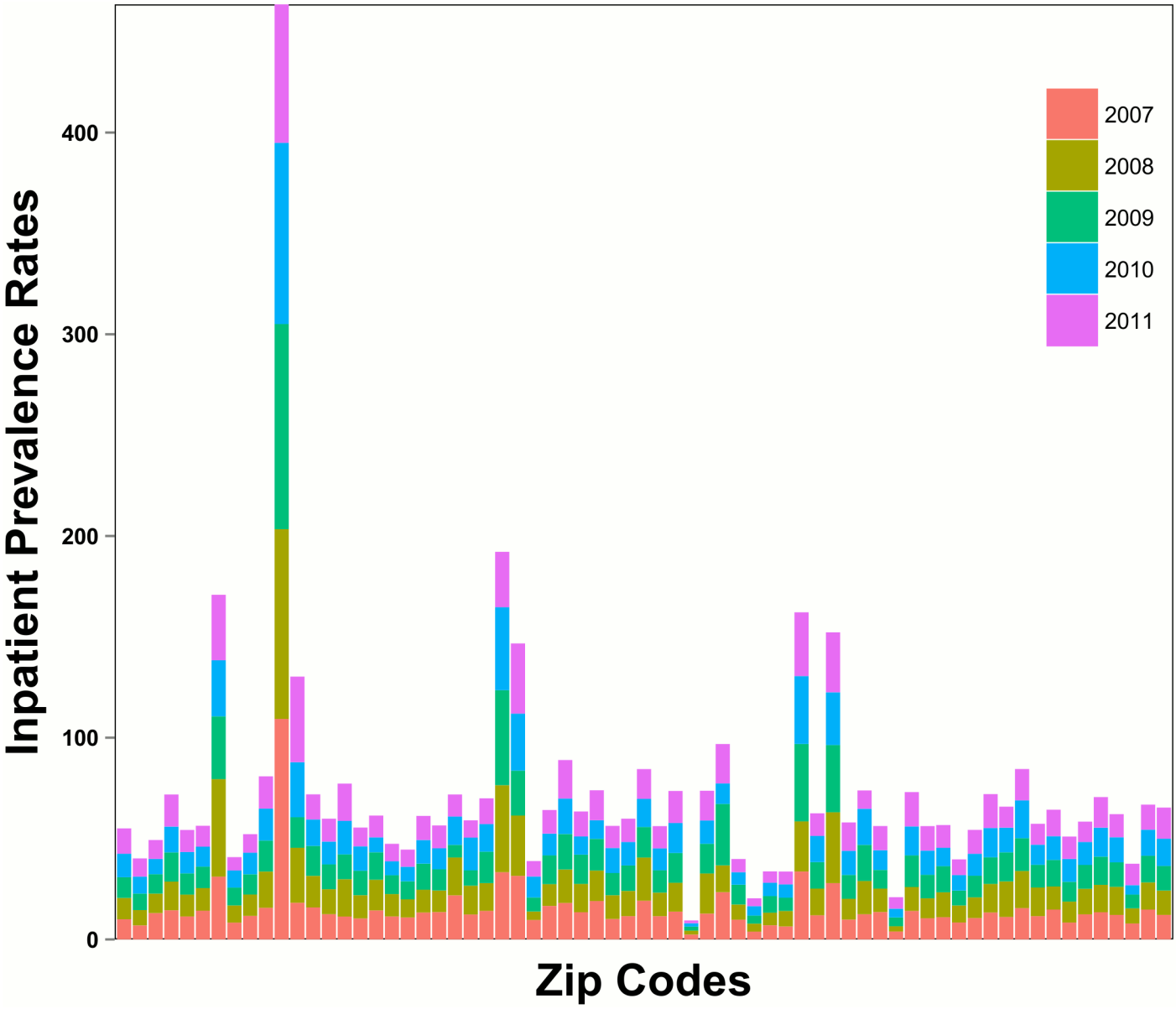


Fig 3. Total inpatient rates by zip code. Total inpatient prevalence rates by zip code. From 2007 to 2011, within a zip code, inpatient prevalence rates are relatively stable.

doi:10.1371/journal.pone.0131093.g003

neurology inpatient prevalence rates were also significantly associated with well density. Also, both sets of analyses show evidence that dermatology, neurology, oncology, and urology inpatient prevalence rates were positively associated with wells. While only the number of wells analyses showed evidence of a positive association between wells and neonatology inpatient prevalence rates, our findings are consistent with other reports suggesting that such illnesses are linked with hydro-fracking [12].

A quadratic association between number of wells and inpatient prevalence rates was also explored. A quadratic relationship seemed to fit the data better than a linear relationship between number of wells and inpatient prevalence rates, within the ophthalmology and neurology categories, where the p-value for the quadratic number of wells term was, respectively, 0.04

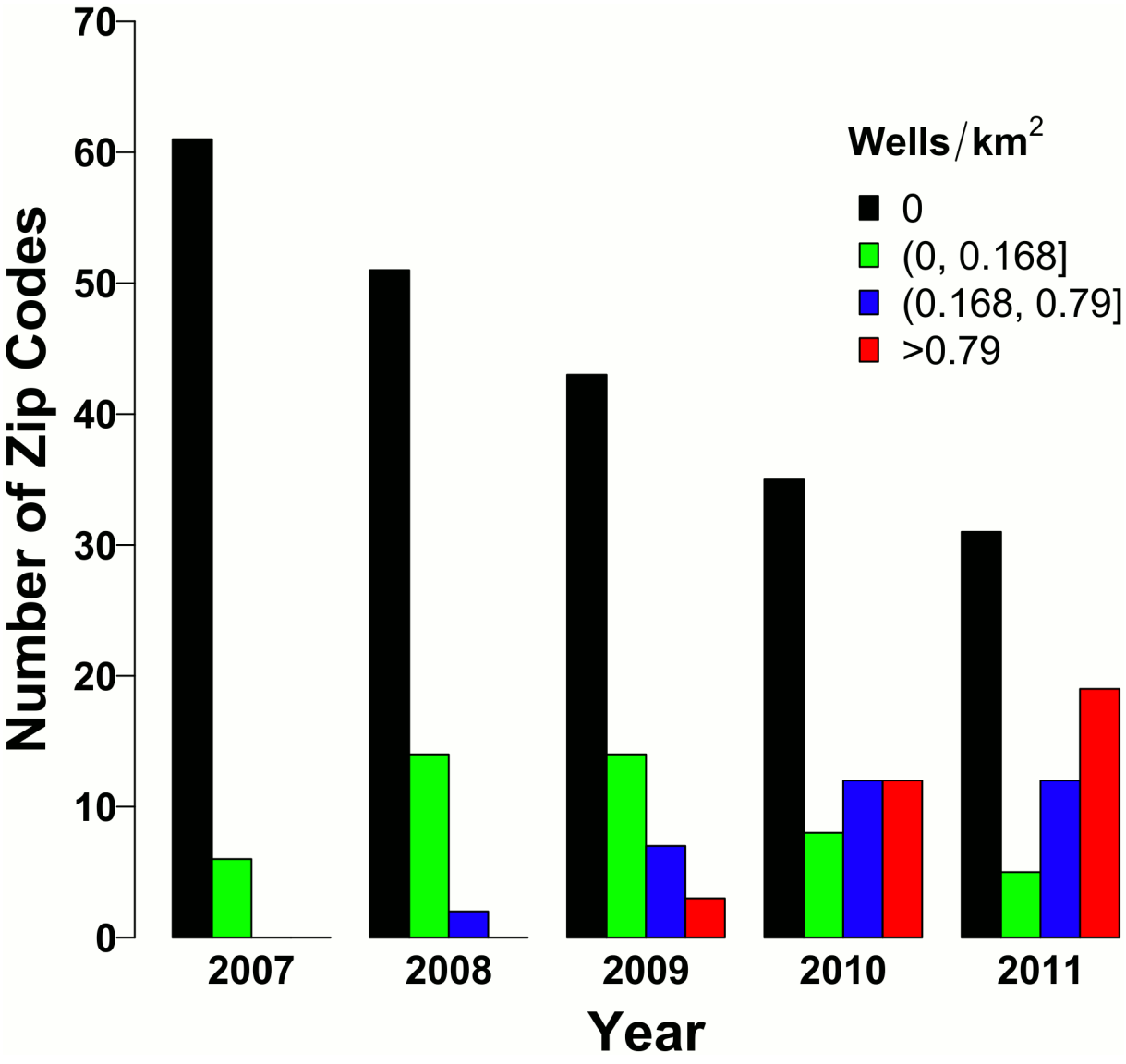


Fig 4. Well density (quantiles) by year. Number of zip codes by well density (quantiles) is presented for each year. In 2007, the majority of zip codes have no wells, but by 2011, the majority of zip codes have at least 1 well.

doi:10.1371/journal.pone.0131093.g004

and 0.004. However, these did not meet the Bonferroni threshold. Furthermore, given Table 3 and the sparsity of ophthalmology inpatient prevalence rates (first three quartiles have no inpatient prevalence rates), it seems unlikely that inference is valid for the ophthalmology models. Given this weak evidence of a quadratic association, results for the quadratic number of wells models are not shown.

In our analysis, one particular zip code had extremely high inpatient prevalence rates compared to other zip codes. Thus, a sensitivity analysis was performed (data not shown). This zip code is located within Wayne County and had no active wells from 2007 to 2011. Removal of this zip code from the analysis had little effect on either the number of wells or the quantile analyses, and there was no change in inference and the estimated risk ratios. Next, a zip code in Bradford had extremely high wells/km^2 in 2010 and 2011, 16.9 wells/km^2 and 23.4 wells/km^2, respectively. Consequently, we explored both sets of analyses without this zip code to

Table 4. Poisson Fixed Effects Models: Number of Wells per Zip Code per Year.

	Wells RR (p-value)	Year RR (p-value)
Inpatient total	1.0003 (0.076)	0.984 (0.128)
Cardiology	**1.0007 (0.0007)**	**0.966 (0.029)**
Dermatology	1.0010 (0.039)	0.977 (0.345)
Endocrine	1.0008 (0.086)	0.963 (0.316)
Gastroenterology	1.0003 (0.338)	0.992 (0.749)
General medicine	1.0002 (0.574)	1.037 (0.022)
Generals surgery	1.0000 (0.849)	1.104 (0.213)
Gynecology	1.0002 (0.708)	0.860 (<0.0001)
Hematology	0.9997 (0.657)	1.023 (0.616)
Neonatology	1.0014 (0.018)	0.959 (0.125)
Nephrology	0.9998 (0.461)	1.025 (0.250)
Neurology	1.0006 (0.037)	1.001 (0.948)
Normal newborns	1.0000 (0.969)	0.963 (0.030)
Ob/delivery	1.0002 (0.411)	0.968 (0.411)
Oncology	1.0015 (0.004)	0.956 (0.081)
Ophthalmology	1.0010 (0.593)	1.084 (0.255)
Orthopedics	0.9993 (0.011)	0.970 (<0.0001)
Other/ob	1.0003 (0.727)	0.899 (0.007)
Otolaryngology	1.0000 (0.982)	0.978 (0.614)
Psych/drug abuse	1.0004 (0.073)	1.035 (0.006)
Pulmonary	1.0000 (0.850)	0.989 (0.482)
Rheumatology	1.0014 (0.043)	0.961 (0.227)
thoracic surgery	1.0011 (0.100)	0.989 (0.708)
Trauma	1.0008 (0.174)	1.021 (0.505)
Urology	1.0010 (0.012)	0.983 (0.464)
Vascular surgery	0.9997 (0.539)	0.948 (0.024)

Note: RR = Risk ratio

doi:10.1371/journal.pone.0131093.t004

determine whether removal of this zip code changed inference. Like the first sensitivity analysis, removal of the Bradford zip code had little effect on inference.

Discussion

We posit that larger numbers of active hydraulic fracturing wells would increase inpatient prevalence rates over time due in part to increases in potential toxicant exposure and stress responses in residents evoked by increases in the hydraulic fracturing work force and diesel engine use. We recognize that a five-year observation period may limit our ability to discern a direct impact on health in the surrounding community but may offer an opportunity to assess hospital utilization rates over time. We examined over 95,000 inpatient records, and thus our study, to our knowledge, represents the most comprehensive one to date to address the health impact of UGOD.

Our data suggests that some but not all medical categories were associated with increases in number of wells, along with increases in well density. Specifically, cardiology inpatient prevalence rates were significantly associated with number of wells and well density, while neurology inpatient prevalence rates were significantly associated with well density. We are struck by the finding that these differences were observable within a short period of time from 2007–2011.

Table 5. Poisson Fixed Effects Models: Quantile Analysis of Wells/km^2.

	Q1 Wells RR (p-value)	Q2 Wells RR (p-value)	Q3 Wells RR (p-value)	Wald Test of all Q Wells = 0	Year RR (p-value)
Inpatient total	0.979 (0.475)	1.069 (0.044)	1.108 (0.041)	P = 0.0058	0.977 (0.013)
Cardiology	**1.021 (0.667)**	**1.142 (0.018)**	**1.27 (0.001)**	**P = 0.0008**	**0.957 (0.004)**
Dermatology	1.051 (0.572)	1.108 (0.429)	1.454 (0.013)	P = 0.0329	0.972 (0.329)
Endocrine	0.975 (0.862)	1.228 (0.045)	1.391 (0.029)	P = 0.0068	0.942 (0.039)
Gastroenterology	0.943 (0.369)	1.12 (0.168)	1.105 (0.364)	P = 0.1101	0.98 (0.406)
General medicine	0.911 (0.234)	0.993 (0.931)	0.985 (0.872)	P = 0.6373	1.037 (0.006)
Generals surgery	0.875 (0.011)	0.921 (0.228)	0.944 (0.424)	P = 0.0669	1.015 (0.157)
Gynecology	0.887 (0.300)	0.938 (0.606)	0.967 (0.849)	P = 0.7549	0.865 (<0.0001)
Hematology	1.202 (0.365)	1.21 (0.320)	1.221 (0.429)	P = 0.7145	0.993 (0.868)
Neonatology	0.994 (0.975)	1.301 (0.152)	1.527 (0.100)	P = 0.0745	0.95 (0.052)
Nephrology	1.115 (0.203)	1.143 (0.227)	1.151 (0.211)	P = 0.5566	1.004 (0.871)
Neurology	**0.922 (0.344)**	**1.157 (0.048)**	**1.188 (0.062)**	**P = 0.0003**	**0.99 (0.542)**
Normal newborns	0.949 (0.481)	0.978 (0.764)	0.964 (0.731)	P = 0.8980	0.965 (0.064)
Ob/delivery	0.958 (0.524)	1.028 (0.670)	1.029 (0.749)	P = 0.4219	0.956 (0.002)
Oncology	1.217 (0.144)	1.415 (0.028)	1.815 (0.002)	P = 0.0166	0.938 (0.022)
Ophthalmology	0.717 (0.381)	1.014 (0.976)	1.116 (0.836)	P = 0.5215	1.099 (0.263)
Orthopedics	0.996 (0.940)	0.981 (0.740)	0.875 (0.130)	P = 0.3591	0.963 (<0.0001)
Other/ob	0.966 (0.885)	1.176 (0.451)	1.264 (0.502)	P = 0.7209	0.879 (0.001)
Otolaryngology	1.052 (0.744)	1.194 (0.412)	1.004 (0.988)	P = 0.5564	0.966 (0.527)
Psych/drug abuse	0.944 (0.307)	0.927 (0.293)	1.13 (0.145)	P = 0.0535	1.039 (0.008)
Pulmonary	1.05 (0.267)	1.097 (0.202)	1.067 (0.572)	P = 0.3050	0.981 (0.306)
Rheumatology	1.091 (0.601)	1.432 (0.159)	1.866 (0.034)	P = 0.0774	0.94 (0.067)
Thoracic surgery	0.872 (0.391)	1.151 (0.470)	1.13 (0.654)	P = 0.0903	0.987 (0.751)
Trauma	0.997 (0.987)	1.057 (0.761)	1.265 (0.222)	P = 0.4373	1.02 (0.562)
Urology	0.827 (0.117)	1.105 (0.462)	1.24 (0.215)	P = 0.0334	0.977 (0.339)
Vascular surgery	1.103 (0.488)	1.052 (0.788)	0.966 (0.857)	P = 0.8116	0.946 (0.030)

Note: RR = Risk ratio

doi:10.1371/journal.pone.0131093.t005

We show that from 2011–2013 (Fig 2) the number of active wells continues to rise exponentially. Although we do not have health care utilization data for 2012–2013, if our findings persisted into 2012–2013, it is possible that the association between cardiology inpatient prevalence rates and wells could only become stronger as a result of the increased number of wells (relative to 2007–2011).

The precise cause for the increase in inpatient prevalence rates within specific medical categories remains unknown. Given that our modeling approach cannot account for within zip code demographic changes over the study period, it is possible that some increases were due to an increased influx of subjects to a zip code. Since the inpatient prevalence rates were determined for subjects *who resided* within a zip code, transient UGOD workers whose address was not local were excluded. Thus, our data potentially may underestimate hospital use that excluded those who were not Pennsylvania residents. Further, our data were partitioned into active wells but it is impossible to associate a specific toxicant exposure to an increase in a specific disease category requiring hospitalization. Intriguingly, our findings partially support those of other studies performed in Colorado. Colburn et al. observed that more than 75% of the chemicals used during natural gas operations may affect skin and respiratory systems, as well as other organs [23]. Another study in Colorado also supports our findings in

neonatology. McKenzie et al. estimate that being within 10 miles of a gas well significantly increased the odds of having a congenital heart defect by 1.3 as well as the odds of having neural tube defects by two-fold, compared to not being within 10 miles of a gas well [12]. A recent study by Lanki et al. determined that living close to busy traffic was associated with increased C-reactive protein (CRP) concentrations, which is a known risk factor for cardiovascular diseases [24]. This supports our results for cardiology, given the increased truck traffic that comes with increased hydro-fracking activity.

Despite our findings that hospitalization use and active well number are directly associated within specific medical categories, there are limitations to our study. Our study examined a relatively short time interval. Whether our findings will be validated over longer periods of observation remains unclear. To have any association within a brief time frame may forebode greater negative health effects over time. Furthermore, with our limited time frame and data, the functional relationship for the association between well density and inpatient prevalence rates was heavily dependent on many extreme values, which make up less than 1% of the total observations. This motivated the quantile analysis. However, there are clear disadvantages to this approach. By partitioning a continuous variable, we inherently lose information. Furthermore, while we can make inference on moving among quantile levels, we cannot make inference for specific increases in well density. The quantile levels were also somewhat arbitrary, characterized as no wells/km^2, a "low" amount of wells/km^2, a "medium amount of wells/km^2, and a "high" amount of wells/km^2. Another possible limitation is that our analyses only considered a zip code "exposed" to wells if there were wells within that specific zip code. A zip code with no wells, however, could neighbor another zip code that has many wells. Accordingly, the association between wells and inpatient prevalence rates may be underestimated. Future work will incorporate a spatial aspect, such that the proximity to exposure (wells) is better addressed. Another limitation is that this study, given that we use hospital discharge data, does not include any information on morbidity or mortality. However, a future study that assesses the association between morbidity/mortality and wells would be interesting to explore.

Despite these limitations, our findings may have a significant impact on the consequences of UGOD on health care delivery and policy. For the number of wells analyses, it is useful to consider specific increases in wells, given that the risk ratio associated with the number of wells predictor is in terms of a one unit increase in number of wells. Specifically, consider an increase of 25 wells, which is the observed mean number of wells from our data. For example, if some zip code had an additional 25 wells, we would expect cardiology inpatient prevalence rates to increase by 2% for that zip code. Considering the quantile analyses, if a zip code went from having zero wells to having greater than 0.79 wells/km^2 (79 wells for each 100 km^2), we would expect cardiology inpatient prevalence rates to increase by 27% for that zip code. If a zip code went from having no wells to having between 0.17 to 0.79 wells/km^2, we then would expect a 14% increase in cardiology inpatient prevalence rates for that zip code. Notably, 18 zip codes had greater than 0.79 wells/km^2, primarily in 2010 and 2011, indicating that each of these zip codes could have had an excess of 27% in cardiology inpatient prevalence rates for each year they had greater than 0.79 wells/km^2. Furthermore, while dermatology and neonatology were not strictly significant after using a Bonferroni correction, there is evidence that dermatology and neonatology inpatient prevalence rates were also positively associated with wells. From the number of wells analyses, if a zip code had an additional 25 wells, we would expect dermatology and neonatology inpatient prevalence rates to increase by 3% and 4%, respectively. Similarly, from the quantile analyses, if a zip code went from having no wells to having greater than 0.79 wells/km^2, we would expect dermatology inpatient prevalence rates to increase by 45% for that zip code.

For most medical categories and overall, given the non-significant year risk ratios from Tables 4 and 5, inpatient prevalence rates remained relatively stable between 2007 and 2011. However, within the medical categories of gynecology and orthopedics, inpatient prevalence rates are expected to decrease each year by around 13–14% and 3–4%, respectively. Despite this surprising result, it is unclear why gynecology and orthopedics inpatient prevalence rates are decreasing each year. It is unlikely that these decreasing rates are related to the increased hydro-fracking activity.

To put into the context the potential burden of hydro-fracking on cardiology hospitalizations, consider the zip codes which exceeded 0.79 wells/km^2 (Q3wells). In total, from 2007 to 2011, three zip codes had >0.79 wells/km^2 in 2009, 10 zip codes had >0.79 wells/km^2 in 2010, and 18 zip codes had >0.79 wells/km^2 in 2011. Some zip codes had >0.79 wells/km^2 in multiple years, and in total, there were 18 unique zip codes that achieved >0.79 wells/km^2 at least once. Of these 31 year/zip code observations, the mean cardiology inpatient prevalence rate was 2.17, the mean number of cardiology inpatient visits was 44.74, and the mean population was 2190. Given the model results from Table 5, if these same observations had no wells, we would have expected the mean cardiology inpatient prevalence rate to be 2.17/1.27 = 1.71. Thus, the expected mean number of cardiology inpatient visits, assuming the mean population, would be 1.71*2190/100 = 37.46. However, this is a slight simplification, since each zip code has a different population. We omit the zip code specific populations to preserve zip code anonymity, but when using zip code specific populations, the expected mean number of cardiology inpatient visits, if these zip codes had no wells, would be 35.23. This means that on average, for any year that a zip code exceeded 0.79 wells/km^2, we would expect an excess of 44.74–35.23 = 9.51 cardiology inpatient visits, compared to if there were no wells. Note that this excess is for a single zip code for a single year in which the zip code exceeded 0.79 wells/km^2 (this occurred 31 times). A similar exercise shows that for zip codes in the Q2wells range (36 observations total), we would expect on average an excess of 8.13 cardiology inpatient rates. This again is for a single zip code for a single year in which the zip code had >0.168 wells/km^2 but ≤0.79 wells/km^2. However, from the model results in Table 5, zip codes with >1 well are in general expected to have increased cardiology inpatient prevalence rates, relative to having no wells. With an inpatient stay costing on average $30K, this poses a significant economic health burden to the Commonwealth of PA.

In summary, hydraulic fracturing as determined by well number or density had a significant association with cardiology inpatient prevalence rates, while well density had a significant association with neurology inpatient prevalence rates. While the clinical significance of the association remains to be shown, UGOD has just begun in Pennsylvania, and thus observing a significant association over this short time is remarkable. Further studies are warranted to compare toxicant exposure to number of wells and inpatient and outpatient studies. Our study also supports the concept that health care utilization should be factored into the value (costs and benefits) of hydraulic fracturing over time.

Supporting Information

S1 Table. ICD-9 diagnosis codes and MSDRGs used in this study. These data are partitioned into three tabs: ICD-9 diagnosis codes, MSDRGs and MSDRG product lines included. (XLSX)

Author Contributions

Conceived and designed the experiments: TJ GLG MH PS TMP KJP RAP. Performed the experiments: TJ GLG MN SC BY MS MH PS NF TMP JR KJP RAP. Analyzed the data: TJ GLG MN SC BY MS NF TMP JR KJP RAP. Contributed reagents/materials/analysis tools: TJ GLG MN SC BY MS MH PS NF TMP JR KJP RAP. Wrote the paper: TJ GLG MN SC BY MS MH PS NF TMP JR KJP RAP.

References

1. IER (2012) U.S. Leads World in Natural Gas Production from Hydraulic Fracturing. Available: http://instituteforenergyresearch.org/analysis/u-s-leads-world-in-natural-gas-production-from-hydraulic-fracturing/#_edn1.
2. EIA (2014) EIA. Annual Energy Outlook 2014. Available: http://www.eia.gov/forecasts/aeo/mt_naturalgas.cfm.
3. Lampe DJ, Stolz JF. Current perspectives on unconventional shale gas extxraction in the Appalachian basin. J Environ Sci Health. 2015; 50: 434–446.
4. Schnoor JL. Shale gas and hydrofracking. Environ Sci Technol. 2012; 46: 4686. doi: 10.1021/es3011767 PMID: 22480196
5. Earthworks. Earthworks Hydraulic Fracturing 101. Available: http://www.earthworksaction.org/issues/detail/hydraulic_fracturing_101#.VSP49PnF98E.
6. EPA (2014) The Process of Hydraulic Fracturing. Available: http://www2.epa.gov/hydraulicfracturing/process-hydraulic-fracturing.
7. Jackson RB, Vengosha A, Darraha TH, Warnera NR. Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. Proc Natl Acad Sci USA. 2013; 110: 11250–11255. doi: 10.1073/pnas.1221635110 PMID: 23798404
8. Gross SA, Avens HJ, Banducci AM, Sahmel J, Panko JM, Tvermoes BE. Analysis of BTEX groundwater concenrations from surface spills associated with hydraulic fracturing operations. J Air Waste Manage Assoc. 2013; 63: 424–432.
9. Warner NR, Christie CA, Jackson RB, Vengosh A. Impacts of shale gas wastewater disposal on water quality in western Pennsylvania. Environ Sci Technol. 2013; 47: 11849–11857. doi: 10.1021/es402165b PMID: 24087919
10. Adgate JL, Goldstein BD, McKenzie LM. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol. 2014; 48: 8307–8320. doi: 10.1021/es404621d PMID: 24564405
11. Macy PG, Breech R, Chernaik M, Cox C, Larson D, Thomas D, et al. Air concentrations of volatile compounds near oil and gas production: a community-based exploratory study. Environmental Health. 2014; 13: 82. doi: 10.1186/1476-069X-13-82 PMID: 25355625
12. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect. 2014; 122: 412–417. doi: 10.1289/ehp.1306722 PMID: 24474681
13. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ. 2012; 424: 79–87. doi: 10.1016/j.scitotenv.2012.02.018 PMID: 22444058
14. Penning TM, Breysse PN, Gray K, Howarth M, Yan B. Environmental Health Research Recommendations from the Inter-Environmental Health Sciences Core Center Working Group on Unconventional Natural Gas Drilling Operations. Environ Health Perspect. 2014; 122: 1155–1159. doi: 10.1289/ehp.1408207 PMID: 25036093
15. Rabinowitz PM, Slizovskiy IB, Lamers V, Trufan SJ, Holford TR, Dziura JD, et al. Proximity to natural gas wells and reported health status: Results of a household survey in Washington County, Pennsylvania. Environ Health Perspect. 2014: Advance Publication 10 September 2014, http://dx.doi.org/2010.1289/ehp.1307732.
16. PA Department of Environmental Protection (2013). Marcellus Shale Development. Available: http://www.elibrary.dep.state.pa.us/dsweb/Get/Document-97683/0100-FS-DEP4217.pdf
17. PA Department of Environmental Protection (2013). 2013 Oil and Gas Annual Report. Available: http://www.portal.state.pa.us/portal/server.pt/community/annual_report/21786
18. MarcellusGas.Org www.marcellusgas.org—Information related to Pennsylvania deep gas well activity.
19. US Government (2010). 2010 Census Data. Available: http://www.census.gov/2010census/data/.

20. PA Departent of Environmental Protection (2014). PA DEP Oil & Gas Reporting Website. Available: https://www.paoilandgasreporting.state.pa.us/publicreports/Modules/DataExports/DataExports.aspx. Pennsylvania Department of Environmental Protection.
21. Wooldridge JM. Distribution-free estimation of some nonlinear panel data models. Journal of Econometrics. 1999; 20: 77–97.
22. Bernstein AB, Hing E, Moss AJ, Allen KF, Siller AB, Tiggle RB. (2003) Health Care in America: Trends in Utilization. In: U.S. Department of Health and Human Services CfDCaP, National Center for Health Statistics, editor. Hyattsville, Maryland: National Center for Health Statistics.
23. Colburn T, Kwiatkowski C, Schultz K, Bachran M. Natural gas operations from a public health perspective. Hum Ecol Risk Assess. 2011; 17: 1039–1056.
24. Lanki T, Hampel R, Tittanen P, Andrich S, Beelen R, Brunekreef B, et al. Air pollution from road traffic and systemic inflammation in adults: a cross-sectional analysis in the European ESCAPE Project. Environ Health Perspect. 2015, Advance Publication 27 March 2015.

American Journal of Epidemiology

Vol. 175, No. 11
DOI: 10.1093/aje/kwr455
Advance Access publication:
April 13, 2012

Original Contribution

Association of Childhood Obesity With Maternal Exposure to Ambient Air Polycyclic Aromatic Hydrocarbons During Pregnancy

Andrew Rundle*, Lori Hoepner, Abeer Hassoun, Sharon Oberfield, Greg Freyer, Darrell Holmes, Marilyn Reyes, James Quinn, David Camann, Frederica Perera, and Robin Whyatt

* Correspondence to Dr. Andrew Rundle, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th Street, Room 730, New York, NY 10032 (e-mail: agr3@columbia.edu).

Initially submitted August 1, 2011; accepted for publication November 9, 2011.

There are concerns that prenatal exposure to endocrine-disrupting chemicals increases children's risk of obesity. African-American and Hispanic children born in the Bronx or Northern Manhattan, New York (1998–2006), whose mothers underwent personal air monitoring for polycyclic aromatic hydrocarbon (PAH) exposure during pregnancy, were followed up to ages 5 ($n = 422$) and 7 ($n = 341$) years. At age 5 years, 21% of the children were obese, as were 25% of those followed to age 7 years. After adjustment for child's sex, age at measurement, ethnicity, and birth weight and maternal receipt of public assistance and prepregnancy obesity, higher prenatal PAH exposures were significantly associated with higher childhood body size. In adjusted analyses, compared with children of mothers in the lowest tertile of PAH exposure, children of mothers in the highest exposure tertile had a 0.39-unit higher body mass index *z* score (95% confidence interval (CI): 0.08, 0.70) and a relative risk of 1.79 (95% CI: 1.09, 2.96) for obesity at age 5 years, and they had a 0.30-unit higher body mass index *z* score (95% CI: 0.01, 0.59), a 1.93-unit higher percentage of body fat (95% CI: 0.33, 3.54), and a relative risk of 2.26 (95% CI: 1.28, 4.00) for obesity at age 7 years. The data indicate that prenatal exposure to PAHs is associated with obesity in childhood.

cohort studies; environment; obesity; pediatrics; polycyclic hydrocarbons, aromatic

Abbreviations: BMI, body mass index; CI, confidence interval; PAH(s), polycyclic aromatic hydrocarbon(s); $PM_{2.5}$, particulate matter less than 2.5 μm in diameter.

Childhood obesity clearly has multiple causes, with the literature identifying proximal, individual-level behavioral risk factors (e.g., high-fat diets, sedentary behavior) and more distal societal-level risk factors affecting diet and physical activity (e.g., suburbanization, automobile dependence, and agricultural policies) (1–3). However, a provocative emerging hypothesis is that exposure to environmental endocrine disruptors plays a role in the obesity epidemic by altering metabolic programming in early life (4–10). The polycyclic aromatic hydrocarbons (PAHs) are a family of chemicals created during incomplete combustion processes and are known human carcinogens that also have endocrine-disrupting effects (11–13). Hydroxy-PAHs, in particular, are structurally similar to estrogen and have been shown to have estrogenic activity in T47D breast adenoma cell lines (ER-CALUX assay; BioDetection Systems, Amsterdam, the Netherlands) (14). Likewise, PAH-containing particulate air pollution has been shown to be estrogenic in the T47D cell line and BG1Luc4E2 ovarian carcinoma cell line and in yeast (14–17). Recent murine and human adipocyte cell culture experiments showed that treatment with benzo[*a*]pyrene, a model PAH, inhibits lipolysis, and recent mouse studies found that benzo[*a*]pyrene exposure caused gains in fat mass (18).

In the Columbia Center for Children's Environmental Health birth cohort study, the Mothers and Children Study in Northern Manhattan and the South Bronx, we investigated the effects of prenatal exposure to airborne PAHs on the child's body size at ages 5 and 7 years and body composition at age 7 years. Because exposures to airborne PAHs were expected to be strongly influenced by individual activities, personal air monitoring was used for exposure assessment (19). Stationary ambient and indoor monitors cannot integrate exposures across times and locations experienced by an individual during a day

in the way that personal monitoring can, and thus personal monitoring is thought to better characterize exposure. Prior analyses of these prenatal air monitoring data found that higher PAH exposures were associated with smaller birth size for gestational age among African Americans (20) and lower full-scale intelligence quotient and verbal intelligence quotient at age 5 years (21).

MATERIALS AND METHODS

Study participants were from a longitudinal birth cohort of mothers and children that has been described extensively elsewhere (22, 23). Nonsmoking pregnant women were recruited through prenatal clinics at New York-Presbyterian Hospital and Harlem Hospital Center between 1998 and 2006. The cohort was restricted to women aged 18–35 years who self-identified as either African-American or Dominican and had resided in Northern Manhattan or the South Bronx in New York City for at least 1 year prior to pregnancy. A questionnaire, administered to each woman in her home by a bilingual interviewer during the third trimester of pregnancy, collected information on demographic characteristics, history of active and passive smoking, educational and income levels, receipt of public assistance during pregnancy, maternal height, and maternal prepregnancy weight. Information on infant sex and birth weight was abstracted from the mothers' and infants' medical records following delivery. Women's home addresses during pregnancy were geocoded, and the physical and sociodemographic characteristics of their neighborhoods, defined as a 1-km radial buffer around the home, were characterized as previously described (24).

As described in detail previously, during the third trimester of pregnancy the women wore a small backpack holding a personal ambient air monitor; the backpack was worn during the daytime for 2 consecutive days, and at night the women placed it near the bed (22, 24). A random subset of backpacks contained motion detectors, and detected motion was consistent with the verbal reports from the subjects that they were wearing the backpacks during daytime hours (21, 23). In ambient air, PAHs are found in vapors and aerosols and are bound to particle matter; particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) is of primary health importance, because fine particles of this size can penetrate deeply into the lungs (25). The personal air sampling pumps operated continuously at 4 L/minute, collecting $PM_{2.5}$ on a precleaned quartz microfiber filter and collecting volatile and semivolatile vapors and aerosols on a polyurethane foam cartridge. Each personal monitoring result was assessed for accuracy in flow rate, time, and completeness of documentation. As described previously (23), particle bound and volatile and semivolatile PAHs were extracted from the filter and polyurethane foam via a Soxhlet Extractor (Corning, Inc., Corning, New York), and extracts were assayed by gas chromatography-mass spectrometry for 8 carcinogenic PAHs: benz[*a*]anthracene, chrysene, benzo[*b*]fluroanthene, benzo[*k*]fluroanthene, benzo[*a*]pyrene, indeno[1,2,3-*cd*]pyrene, dibenz[*a*,*h*]anthracene, and benzo[*g*,*h*,*i*]perylene. Comparisons between PAH levels measured in these air samples and levels measured in other cities have been reported previously (19). A substudy of 84 women was conducted to measure pollutants in residential indoor air during the last 6–8 weeks of pregnancy (26). Personal air samples were collected from the mothers over a period of 48 hours during the 32nd week of pregnancy, and then 2-week integrated indoor residential air samples were collected sequentially for the remaining 6–8 weeks of the pregnancy (26). Personal and indoor air samples were analyzed for PAHs using the same methods as in the full study (23).

Personal air monitoring and measurement of PAHs was completed for 702 women; 511 of the children born to these women have been followed up to age 5 years, and thus far (as of 2011) 391 children have been followed up to age 7 years. Height and weight data were collected from 453 of the children at age 5 years and from 371 of the children at age 7 years, and body composition data were collected from 324 of these children. Figure 1 documents follow-up and attrition.

Weight at age 5 years was measured to the nearest 0.1 kg using a Detecto Cardinal 750 digital scale (Cardinal Scale Manufacturing Company, Webb City, Missouri) while the child was wearing light clothes and no shoes. At age 7 years, weight (to the nearest 0.1 kg) and body composition were measured using a Tanita scale (model BC-418; Tanita Corporation of America, Arlington Heights, Illinois). The Tanita scale reported percentage of body fat, fat mass, and lean mass using bioimpedance formulas validated in children as young as age 7 years. Height (to the nearest 0.1 cm) was measured using a SECA wall-mounted stadiometer (SECA, Hamburg, Germany).

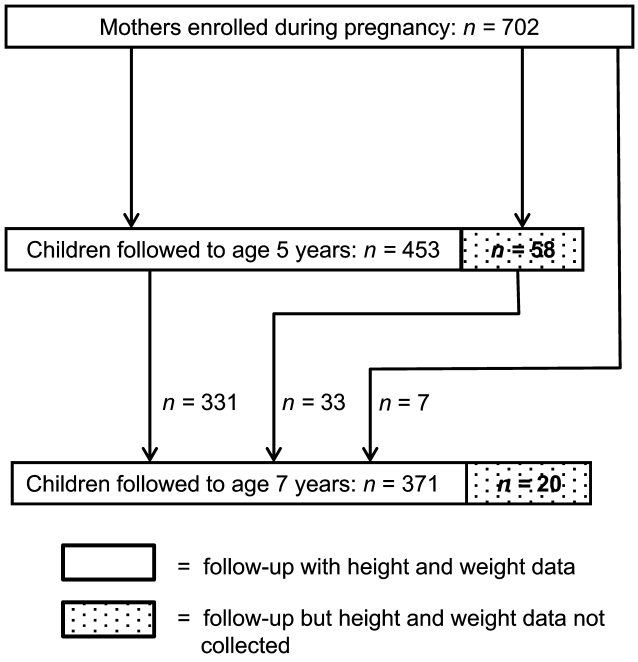


Figure 1. Follow-up of children from a New York City birth cohort at ages 5 and 7 years and from whom height and weight data were collected, Mothers and Children Study in Northern Manhattan and the South Bronx, 1998–2011. Some children who were not followed up to age 5 years ($n = 7$) or from whom height and weight data were not collected at age 5 years ($n = 33$) were followed up at age 7 years and were measured for height and weight.

Data analyses

Concentrations of the 8 PAHs measured in the air samples were summed and natural log-transformed (21, 23). Log-transformed personal air PAH levels were compared via *t* test across categories of obesity risk factors for the entire cohort and for children from whom anthropometric data were collected at ages 5 and 7 years. For the indoor air PAH exposure substudy, intraclass correlation coefficients were calculated to assess the variability of the integrated indoor air monitoring data during the last 6–8 weeks of pregnancy. Correlation coefficients were calculated comparing the mean residential indoor air PAH exposure calculated from the sequential 2-week indoor air monitoring with the 48-hour personal air monitoring data.

Children's body mass index (BMI; weight (kg)/height $(m)^2$) *z* scores and percentiles were calculated using the Centers for Disease Control and Prevention SAS macro (27); children were classified as obese if their BMI percentile was greater than or equal to the 95th percentile. Children were assigned to low, medium, and high maternal prenatal exposure categories based on tertile cutpoints of the distribution of prenatal PAH exposure levels. A series of linear regression analyses was used to determine whether children whose mothers were in the second (middle) or third (highest) tertile of personal air exposure to PAHs as compared with the first (lowest) tertile had higher BMI *z* scores at ages 5 and 7 years and a higher percentage of body fat, total fat mass, and fat-free mass at age 7 years. Relative risks of obesity at ages 5 and 7 years by exposure tertile were estimated using Poisson regression models (28, 29). All analyses controlled for the child's sex, age at anthropometric measurement, ethnicity, and birth weight and maternal prepregnancy obesity. Measures of the mother's socioeconomic status during pregnancy, including self-reported family income, mother's educational attainment, and receipt of public assistance, were assessed as potential confounders. Receipt of public assistance was found to be the only predictor of the anthropometric outcomes and was included in all statistical models.

Additional sensitivity analyses were conducted assessing prenatal factors that might affect children's growth trajectories and are also thought to be related to PAH exposure: season of monitoring, the mother's living with a smoker, the mother's living in a neighborhood with a high level of automobile traffic, and neighborhood socioeconomic status. Monitoring periods were classified as to whether or not they occurred between October 15 and April 31, the dates when owners of New York City apartment buildings are required to provide heat, predominantly via oil-fueled furnaces. Questionnaire data were used to assess whether a mother had lived with a smoker during her pregnancy. As a measure of exposure to automobile traffic, street density (linear distance of streets/area of neighborhood) within a 1-km radial buffer around the mother's residence during pregnancy was measured. Neighborhood socioeconomic status was measured using 2000 US Census block group data on poverty and median household income aggregated to the 1-km radial neighborhood buffers using aerial weighting interpolation (24, 30). As described in prior work, for analyses that included neighborhood-level variables, linear regression generalized estimating equations with robust standard error calculations were used to account for clustering of subjects within New York City Community District neighborhoods (24, 31). In addition, analyses were conducted using inverse probability weights for successful follow-up and complete data collection to assess the effects of incomplete follow-up and missing data on effect estimates (32–34). These analyses are described in detail in the Web Appendix (http://aje.oxfordjournals.org/).

All study procedures used at enrollment and at ages 5 and 7 years were approved by the Columbia University Institutional Review Board. Informed consent was obtained from all participating women, and assent was provided by the children at age 7 years.

RESULTS

Table 1 shows the geometric mean levels of PAH exposure overall and by categories of obesity risk factors for the entire cohort and for children at ages 5 and 7 years. For the cohort overall, mothers receiving public assistance had significantly higher exposure levels, and for children followed up to age 5 years, mothers of African-American children had higher exposure levels than mothers of Dominican children. In the indoor air monitoring substudy, the intraclass correlation coefficient for the consecutive 2-week indoor air sampling periods was 0.65 during the last 6–8 weeks of pregnancy. Estimates of prenatal PAH exposure based on individual 48-hour personal air monitoring and based on the mean of the consecutive 2-week integrated indoor air monitoring periods were significantly correlated ($r = 0.58$, $P < 0.001$).

Complete data for outcomes and key covariates (sex, ethnicity, receipt of public assistance during pregnancy, birth weight, and maternal prepregnancy obesity) were available from 422 of the 453 children followed to age 5 years for anthropometric outcomes and from 341 of the 371 children followed to age 7 years. Data on body composition and key covariates were available for 297 children. The primary missing data element was maternal prepregnancy weight. Table 2 presents descriptive statistics for the sociodemographic characteristics and risk factors for all cohort children at baseline and for those followed up. At age 5 years, 21% of the children were obese, and at age 7 years, 25% were obese; the mean percentage of body fat at age 7 years was 24.1% (7.2 kg of fat mass). As expected, for the 331 children from whom anthropometric data were available at ages 5 and 7 years, obesity at age 5 was strongly predictive of obesity at age 7 ($\kappa = 0.67$, $P < 0.001$; relative risk = 8.39, 95% confidence interval (CI): 5.63, 12.50).

In unadjusted analyses, compared with children whose mothers were in the first tertile of prenatal PAH exposure, at age 5 years the BMI *z* score was 0.33 units higher (95% CI: 0.02, 0.65) for children of mothers in the second exposure tertile, and it was 0.43 units higher (95% CI: 0.12, 0.75) for children of mothers in the third exposure tertile. Similar effects were seen at age 7 years; compared with the first tertile, the second tertile of exposure was associated with a 0.17-unit higher BMI *z* score (95% CI: −0.14, 0.48), and the third tertile of exposure was associated with a 0.32-unit higher BMI *z* score (95% CI: 0.01, 0.62).

Table 3 shows the multivariate associations between model covariates and categories of maternal PAH exposure

Table 1. Geometric Mean Levels (ng/m^3) of Polycyclic Aromatic Hydrocarbons in Prenatal Personal Air Monitoring Samples in the Mothers and Children Study in Northern Manhattan and the South Bronx, 1998–2011

Characteristic	Total Enrolled Cohort (n = 702)	Children With Anthropometric Measures at Age 5 Years (n = 453)	Children With Anthropometric Measures at Age 7 Years (n = 371)
Overall	2.39 (2.12)[a]	2.34 (2.05)	2.53 (2.03)
Child's sex			
Girls	2.34 (2.08)	2.34 (1.99)	2.53 (1.97)
Boys	2.44 (2.18)	2.32 (2.14)	2.53 (2.10)
Child's ethnicity			
African-American	2.53 (2.01)	2.53 (1.90)	2.69 (1.92)
Dominican	2.29 (2.18)	2.20 (2.16)*	2.44 (2.10)
Maternal prepregnancy obesity			
No	2.39 (2.23)	2.29 (2.14)	2.53 (2.08)
Yes	2.36 (1.93)	2.56 (1.92)	2.69 (1.93)
Maternal receipt of public assistance during pregnancy			
No	2.25 (2.14)	2.25 (2.08)	2.44 (2.03)
Yes	2.53 (2.08)*	2.46 (2.05)	2.66 (2.03)

* $P < 0.05$ (by t test).
[a] Numbers in parentheses, standard deviation.

and BMI z score and body composition measures. After control for the model covariates, the highest tertile of prenatal PAH exposure was significantly associated with higher BMI z score at both age 5 years and age 7 years. In addition, at age 7 years, higher prenatal PAH exposure was significantly associated with increased percentage of body fat and fat mass but not with variation in lean mass (e.g., organs, bone, and muscle). Figure 2 shows the covariate-adjusted mean BMI z scores (and 95% confidence intervals) at ages 5 and 7 years by tertile of prenatal PAH exposure. To place the results in context, for a 5-year-old boy with a weight of 21 kg and a height of 115 cm (BMI z score = 0.37, BMI percentile = 64.5—median values for the study population), an increase of 0.39 z-score units equates to a 0.7-kg increase in weight and a 13-unit increase in BMI percentile. Similarly, for a 7-year-old boy with a weight of 27 kg and a height of 126 cm (BMI z score = 0.86, BMI percentile = 80.5), an increase of 0.30 z-score units equates to a 1.11-kg increase in weight and places the child at the 87.7th BMI percentile. Being in the third tertile of prenatal PAH exposure as compared with the first was associated with 1.1-kg higher fat mass. Table 4 shows that the second and third tertiles of maternal PAH exposure were associated with higher relative risks of obesity at ages 5 and 7 years.

We conducted further analyses to assess the sensitivity of the results to additional model specifications and adjustment for other covariates. Neighborhood socioeconomic status represents a potential confounding factor; however, further control for neighborhood poverty rate or median household income did not alter the results. In regards to factors hypothesized to be associated with higher ambient air PAH levels, PAH levels were not associated with the mother's reporting that a smoker lived in the home or with neighborhood socioeconomic status. Air monitoring samples collected during heating months showed 47% higher PAH levels (95% CI: 29, 67) than samples collected during the nonheating months, and higher PAH levels were associated with higher street density within a 1-km radius of the home (2.94% higher per linear kilometer of street; 95% CI: 0.20, 5.65). However, season of sampling and neighborhood street density did not predict BMI z score at age 5 or 7 years or body composition at age 7 years, and adjustment for these variables did not alter the analytical results.

Weighting the data by the inverse probability of follow-up and complete data collection at age 5 years only slightly reduced the estimated effect of the third tertile of PAH exposure on BMI z score (weighted estimate = 0.34 BMI z-score units; 95% CI: 0.02, 0.66) and did not alter the effect estimate for the second tertile of exposure. However, inverse probability-weighted analyses for BMI z score at age 7 years suggested that the initial analyses were biased toward the null value. Compared with the first tertile of PAH exposure, the covariate-adjusted weighted β coefficient for the second tertile of exposure was 0.28 BMI z-score units (95% CI: −0.01, 0.58), while in the unweighted analyses the covariate-adjusted coefficient was 0.17 units (95% CI: −0.12, 0.46). For comparisons between the third and first tertiles of exposure, the covariate-adjusted weighted β coefficient was 0.40 BMI z-score units (95% CI: 0.11, 0.69), while the corresponding covariate-adjusted coefficient in the unweighted analyses was 0.30 BMI z-score units (95% CI: 0.01, 0.58).

DISCUSSION

Prenatal exposure to ambient PAHs was found to predict higher BMI z score and obesity at age 5 years and higher BMI z score, obesity, and fat mass at age 7 years. The observed effect of prenatal exposure to PAHs on children's body size appears to be due to the accumulation of fat mass and not to differences in lean mass. In our analyses, we considered possible confounding by measures of socioeconomic status and by prenatal exposure to sources of PAHs and found that adjustment

Table 2. Sociodemographic and Anthropometric Characteristics of the Cohort at Baseline and During Follow-up, Mothers and Children Study in Northern Manhattan and the South Bronx, 1998–2011

Characteristic	Total Enrolled Cohort ($n = 702$)			Children With Anthropometric Measures at Age 5 Years ($n = 453$)			Children With Anthropometric Measures at Age 7 Years ($n = 371$)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Child's sex									
Female	352	50		240	53		200	54	
Male	335	48		213	47		171	46	
Unknown	15	2		0			0		
Child's ethnicity									
African-American	256	37		185	41		160	43	
Dominican	446	63		268	59		211	57	
Child's birth weight, g			3,369 (477)			3,380 (480)			3,406 (486)
Maternal prepregnancy obesity									
No	499	71		330	73		269	73	
Yes	166	24		101	22		81	22	
Unknown	37	5		22	5		21	6	
Maternal receipt of public assistance during pregnancy									
No	402	57		255	56		211	57	
Yes	294	42		194	43		156	42	
Unknown	6	1		4	1		4	1	
Mother's years of education at time of pregnancy			12 (2)			12 (2)			12 (2)
% of residents living in poverty in the mother's neighborhood			36 (5)			35 (5)			35 (4)
Annual household income in the mother's neighborhood, dollars			22,661 (3,621)			22,489 (3,430)			22,517 (3,285)
Geometric mean PAH level in personal air monitoring samples, ng/m^3			2.38 (2.13)			2.34 (2.06)			2.54 (2.03)
Body mass index[a] *z* score			NA			0.64 (1.37)			0.82 (1.15)
Childhood obesity									
No	NA			356	79		277	75	
Yes	NA			97	21		94	25	
Mean % of body fat ($n = 324$)			NA			NA			24 (6)

Abbreviations: NA, not applicable; PAH, polycyclic aromatic hydrocarbon; SD, standard deviation.
[a] Weight (kg)/height (m)^2.

for these factors did not alter the results. Similar to a prior report using data from midway through cohort recruitment, the mother's report of a smoker living in the home did not predict PAH levels in the prenatal air monitoring samples (19). Season of monitoring and neighborhood street density did predict PAH levels, but not body size at ages 5 and 7 years. These results provide the first evidence that childhood obesity can be influenced by prenatal exposure to PAHs.

These results are consistent with past laboratory experiments showing PAH and particulate air pollution effects on lipolysis and fat accumulation. Murine and human adipocyte experiments showed that treatment with benzo[*a*]pyrene, a model PAH, suppressed the normal release of free fatty acids by adipocytes upon exposures to β_1, β_2, and β_3-adrenoreceptor-specific agonists (18). Similarly, C57Bl/6J mouse experiments showed that benzo[*a*]pyrene treatment inhibited epinephrine-induced release of free fatty acids, and 15 days of chronic exposure caused weight gain due to accumulation of fat mass (18). A second study found that starting at week 3 of life, 10 weeks of exposure to a $PM_{2.5}$ particle mixture representative of the northeastern region of the United States caused weight gain in C57Bl/6J mice due to increases in subcutaneous and visceral fat mass, although $PM_{2.5}$ exposure concentrations were 10-fold higher than ambient levels (35, 36). Cigarette smoke is a source of PAHs, and maternal smoking during pregnancy has consistently been found to be associated with higher body weight in the child during childhood and adolescence and into adulthood (37, 38). While the literature on maternal smoking during pregnancy tends to ascribe smoking's

Table 3. Associations of Prenatal Exposure to Polycyclic Aromatic Hydrocarbons and Sociodemographic and Early-Life Characteristics With Body Size and Composition at Ages 5 and 7 Years Among Children in the Mothers and Children Study in Northern Manhattan and the South Bronx, 1998–2011[a]

Risk Factor	BMI[b] *z* Score at Age 5 Years		BMI *z* Score at Age 7 Years		% Body Fat at Age 7 Years		Fat Mass at Age 7 Years, kg		Fat-Free Mass at Age 7 Years, kg	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Birth weight (per 100 g)	0.05	0.02, 0.08	0.04	0.02, 0.07	0.14	0.00, 0.27	0.11	0.03, 0.20	0.18	0.10, 0.26
Ethnicity										
Dominican	0	Reference	0	Reference	0	Reference	0	Reference	0	Reference
African-American	−0.10	−0.37, 0.17	−0.11	−0.35, 0.14	−1.59	−2.97, −0.21	−0.60	−1.46, 0.26	0.16	−0.65, 0.99
Maternal receipt of public assistance during pregnancy										
No	0	Reference	0	Reference	0	Reference	0	Reference	0	Reference
Yes	−0.07	−0.32, 0.19	−0.20	−0.43, 0.04	−1.38	−2.70, −0.05	−1.05	−1.88, −0.23	−0.79	−1.57, −0.01
Child's sex										
Female	0	Reference	0	Reference	0	Reference	0	Reference	0	Reference
Male	0.02	−0.23, 0.27	0.19	−0.05, 0.42	−1.61	−2.92, −0.30	−0.23	−1.05, 0.59	1.08	0.31, 1.85
Maternal prepregnancy obesity										
No	0	Reference	0	Reference	0	Reference	0	Reference	0	Reference
Yes	0.38	0.07, 0.68	0.72	0.44, 1.00	3.85	2.27, 5.44	2.41	1.42, 3.40	1.91	0.98, 2.85
Child's age at measurement, months	0.06	0.01, 0.11	0.01	−0.04, 0.06	0.09	−0.18, 0.36	0.15	−0.02, 0.32	0.26	0.10, 0.42
Tertile of prenatal PAH exposure										
First (<1.73 ng/m^3)	0	Reference	0	Reference	0	Reference	0	Reference	0	Reference
Second (1.73–3.07 ng/m^3)	0.26	−0.05, 0.57	0.17	−0.13, 0.46	1.91	0.27, 3.55	1.19	0.17, 2.22	0.45	−0.52, 1.41
Third (≥3.08 ng/m^3)	0.39	0.08, 0.70	0.30	0.01, 0.59	1.93	0.33, 3.54	1.11	0.10, 2.11	0.34	−0.61, 1.29

Abbreviations: BMI, body mass index; CI, confidence interval; PAH, polycyclic aromatic hydrocarbon.

[a] All linear regression β coefficients predicting the anthropometric outcomes were mutually adjusted for the other predictor variables in the table.

[b] Weight (kg)/height (m)^2.

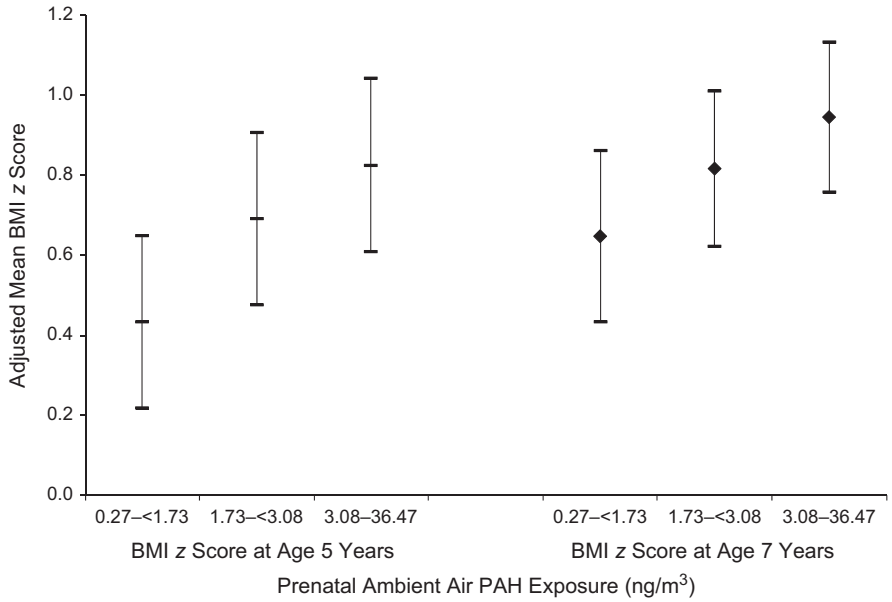


Figure 2. Covariate-adjusted mean body mass index (BMI; weight (kg)/height (m)^2) *z* scores according to tertile of prenatal ambient air polycyclic aromatic hydrocarbon (PAH) exposure for children at ages 5 and 7 years, Mothers and Children Study in Northern Manhattan and the South Bronx, 1998–2011. Median PAH exposure levels for tertile categories: first tertile, 1.19 ng/m^3; second tertile, 2.30 ng/m^3; third tertile, 4.68 ng/m^3. Bars, 95% confidence interval.

Table 4. Risks of Obesity at Ages 5 and 7 Years According to Prenatal Exposure to Polycyclic Aromatic Hydrocarbons and Sociodemographic and Early-Life Characteristics Among Children in the Mothers and Children Study in Northern Manhattan and the South Bronx, 1998–2011

	Obesity at Age 5 Years		Obesity at Age 7 Years	
	RR[a]	95% CI	RR[a]	95% CI
Birth weight (per 100 g)	1.04	1.00, 1.08	1.02	0.98, 1.06
Ethnicity				
Dominican	1	Reference	1	Reference
African-American	0.68	0.45, 1.01	0.72	0.49, 1.06
Maternal receipt of public assistance during pregnancy				
No	1	Reference	1	Reference
Yes	0.94	0.65, 1.36	0.78	0.54, 1.13
Child's sex				
Female	1	Reference	1	Reference
Male	1.01	0.70, 1.44	1.28	0.90, 1.82
Maternal prepregnancy obesity				
No	1	Reference	1	Reference
Yes	1.39	0.93, 2.08	2.01	1.39, 2.92
Child's age at measurement, months	1.05	1.00, 1.10	1.04	0.97, 1.11
Tertile of prenatal PAH exposure				
First (<1.73 ng/m^3)	1	Reference	1	Reference
Second (1.73–3.07 ng/m^3)	1.79	1.08, 2.98	2.25	1.27, 4.01
Third (≥3.08 ng/m^3)	1.79	1.09, 2.96	2.26	1.28, 4.00

Abbreviations: CI, confidence interval; PAH, polycyclic aromatic hydrocarbon; RR, relative risk.
[a] All relative risks were mutually adjusted for other variables in the table.

effects on children's weight to nicotine exposure, it is possible that it is the PAH component of cigarette smoke that affects the children's growth trajectory (37).

Recently, substantial attention has been focused on the hypothesis that prenatal and early-life exposure to environmental estrogens causes obesity (7–10, 39). Studies with CD-1 mice have shown that treatment during the neonatal period with diethylstilbestrol, a model estrogenic compound, causes increased weight gain (8). Although PAHs have been referred to as xenoestrogens, both estrogenic and antiestrogenic effects have been documented, with the primary endocrine effect relating to interference with estrogen signaling (11, 12). The effects of PAHs on estrogen receptor-mediated signaling have been shown to be compound-specific and cellular model-dependent (12). However, studies have shown that PAHs induce estrogen-dependent cell proliferation and estrogen receptor-mediated reporter gene expression and that they induce uterine growth in Wistar rats (12, 40, 41). Hydroxy-PAHs, in particular, have structural similarities to estrogen, and in vitro test systems have shown them to have estrogenic activity; in addition, PAH-containing particulate air pollution has been shown to have estrogenic effects in estrogen-responsive carcinoma cell lines and in yeast models (14–17). PAHs may also alter estrogen signaling through crosstalk between the estrogen receptor and the aryl hydrocarbon receptor, for which PAHs are a ligand (42). In human breast tissue, we have shown that levels of PAH-DNA adducts in breast tumors are significantly correlated with estrogen receptor expression (43). However, data are not available for testing whether weight gain associated with PAH exposure is mediated via an estrogen receptor agonist-based mechanism.

Several caveats must be considered when interpreting these results. Firstly, the study was restricted to nonsmoking women and so may not be generalizable to women who smoke during pregnancy. The personal air monitoring was conducted for only 48 hours in the third trimester, and PAH levels detected during this short duration of monitoring may not be representative of longer-term exposures incurred during pregnancy. However, the indoor air monitoring substudy showed that residential indoor PAH exposure levels were fairly stable during the last 6–8 weeks of pregnancy and that home indoor PAH levels were correlated with those in the personal air monitoring samples. Secondly, we were not able to adjust for ambient air PAH exposures in early childhood prior to age 5 years, which may be correlated with the mother's exposures during pregnancy. Thus, it is not absolutely clear that pregnancy is the critical exposure window, and we may be indirectly observing the effects of early childhood exposures on subsequent growth trajectories. Body composition was measured using Tanita bioimpedance technology and a 2-compartment model of the body, which, while it has been validated (44–48), still represents a clinical standard rather than a gold-standard, 4-compartment measure of body composition. Additionally, the Tanita bioimpedance technology is not recommended for assessing body composition in children before age 7 years; thus, fat and lean mass data were not gathered at age 5 years. Lastly, follow-up was not complete, particularly to age 7 years, and it was associated with several predictors of body size. However, reanalysis of the data using inverse probability weighting for successful follow-up suggested that incomplete follow-up did not bias the age 5 results and that it caused a bias toward the null for the age 7 results (32, 33).

In conclusion, this study suggests that prenatal exposure to PAHs causes increased fat mass gain during childhood and a higher risk of childhood obesity. The strengths of this study include the use of personal air monitoring to measure exposure to PAHs during pregnancy, the prospective cohort design, and the use of body composition data to demonstrate specific effects on fat mass. These results provide further data on the negative health consequences of air pollution and suggest that prenatal exposure to endocrine-disrupting chemicals contributes to obesity risk.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York (Andrew Rundle); Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York (Lori Hoepner, Greg Freyer, Darrell Holmes, Marilyn Reyes, Frederica Perera, Robin Whyatt); Department of Pediatrics, New York-Presbyterian Hospital, Columbia University, New York, New York (Abeer Hassoun, Sharon Oberfield); Institute for Social and Economic Research and Policy, Columbia University, New York, New York (James Quinn); and Southwest Research Institute, San Antonio, Texas (David Camann).

This study was supported by the National Institute of Environmental Health Sciences (grants 5P01ES09600, 5R01ES08977, R01ES010165, and R01ES015282), the Environmental Protection Agency (grants R827027, 8260901, and RR00645), the Educational Foundation of America, the John and Wendy Neu Family Foundation, the New York Community Trust, and the Trustees of the Blanchette Hooker Rockefeller Fund.

Conflict of interest: none declared.

REFERENCES

1. Sallis JF, Cervero RB, Ascher W, et al. An ecological approach to creating active living communities. *Annu Rev Public Health*. 2006;27:297–322.
2. Sallis JF, Glanz K. The role of built environments in physical activity, eating, and obesity in childhood. *Future Child*. 2006;16(1):89–108.
3. Sallis JF, Glanz K. Physical activity and food environments: solutions to the obesity epidemic. *Milbank Q*. 2009;87(1):123–154.
4. Grün F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. 2006;147(6 suppl):S50–S55.
5. Grün F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. *Rev Endocr Metab Disord*. 2007;8(2):161–171.
6. Grün F, Blumberg B. Minireview: the case for obesogens. *Mol Endocrinol*. 2009;23(8):1127–1134.
7. Newbold RR, Padilla-Banks E, Jefferson WN, et al. Effects of endocrine disruptors on obesity. *Int J Androl*. 2008;31(2):201–208.

8. Newbold RR, Padilla-Banks E, Snyder RJ, et al. Perinatal exposure to environmental estrogens and the development of obesity. *Mol Nutr Food Res*. 2007;51(7):912–917.
9. Newbold RR, Padilla-Banks E, Snyder RJ, et al. Developmental exposure to endocrine disruptors and the obesity epidemic. *Reprod Toxicol*. 2007;23(3):290–296.
10. Heindel JJ. Endocrine disruptors and the obesity epidemic. *Toxicol Sci*. 2003;76(2):247–249.
11. Davis DL, Bradlow HL, Wolff M, et al. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. *Environ Health Perspect*. 1993;101(5):372–377.
12. Kummer V, Masková J, Zralý Z, et al. Estrogenic activity of environmental polycyclic aromatic hydrocarbons in uterus of immature Wistar rats. *Toxicol Lett*. 2008;180(3): 212–221.
13. Santodonato J. Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere*. 1997;34(4):835–848.
14. Wenger D, Gerecke AC, Heeb NV, et al. In vitro estrogenicity of ambient particulate matter: contribution of hydroxylated polycyclic aromatic hydrocarbons. *J Appl Toxicol*. 2009;29(3): 223–232.
15. Klein GP, Hodge EM, Diamond ML, et al. Gas-phase ambient air contaminants exhibit significant dioxin-like and estrogen-like activity in vitro. *Environ Health Perspect*. 2006;114(5): 697–703.
16. Wang J, Wu W, Henkelman B, et al. Presence of estrogenic activity from emission of fossil fuel combustion as detected by a recombinant yeast bioassay. *Atmos Environ*. 2003;37(23): 3225–3235.
17. Wang J, Xie P, Kettrup A, et al. Inhibition of progesterone receptor activity in recombinant yeast by soot from fossil fuel combustion emissions and air particulate materials. *Sci Total Environ*. 2005;349(1–3):120–128.
18. Irigaray P, Ogier V, Jacquenet S, et al. Benzo[*a*]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. *FEBS J*. 2006;273(7): 1362–1372.
19. Tonne CC, Whyatt RM, Camann DE, et al. Predictors of personal polycyclic aromatic hydrocarbon exposures among pregnant minority women in New York City. *Environ Health Perspect*. 2004;112(6):754–759.
20. Choi H, Rauh V, Garfinkel R, et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. *Environ Health Perspect*. 2008;116(5): 658–665.
21. Perera FP, Li Z, Whyatt R, et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics*. 2009;124(2):e195–e202.
22. Whyatt RM, Barr DB, Camann DE, et al. Contemporary-use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority mothers and newborns. *Environ Health Perspect*. 2003;111(5):749–756.
23. Perera FP, Rauh V, Tsai WY, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect*. 2003;111(2): 201–205.
24. Lovasi GS, Quinn JW, Rauh VA, et al. Chlorpyrifos exposure and urban residential environment characteristics as determinants of early childhood neurodevelopment. *Am J Public Health*. 2011; 101(1):63–70.
25. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287(9):1132–1141.
26. Whyatt RM, Garfinkel R, Hoepner LA, et al. Within- and between-home variability in indoor-air insecticide levels during pregnancy among an inner-city cohort from New York City. *Environ Health Perspect*. 2007;115(3):383–389.
27. Centers for Disease Control and Prevention. *A SAS Program for the CDC Growth Charts*. Atlanta, GA: Centers for Disease Control and Prevention; 2004.
28. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7): 702–706.
29. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005;162(3): 199–200.
30. Flowerdew R, Green M. Data integration: statistical methods for transferring data between zonal systems. In: Masser I, Blakemore M, eds. *Handling Geographical Information: Methodology and Potential Applications*. New York, NY: Longman Publisher's; 1991:38–54.
31. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology*. 2010;21(4):467–474.
32. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5): 615–625.
33. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550–560.
34. Curtis LH, Hammill BG, Eisenstein EL, et al. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007; 45(10 suppl 2):S103–S107.
35. Xu X, Yavar Z, Verdin M, et al. Effect of early particulate air pollution exposure on obesity in mice: role of p47phox. *Arterioscler Thromb Vasc Biol*. 2010;30(12):2518–2527.
36. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA*. 2005;294(23):3003–3010.
37. Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *Int J Obes (Lond)*. 2008;32(2):201–210.
38. Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. *Int J Epidemiol*. 2002;31(2): 413–419.
39. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. *Mol Cell Endocrinol*. 2009;304(1-2): 84–89.
40. Abdelrahim M, Ariazi E, Kim K, et al. 3-Methylcholanthrene and other aryl hydrocarbon receptor agonists directly activate estrogen receptor alpha. *Cancer Res*. 2006;66(4):2459–2467.
41. Tsai KS, Yang RS, Liu SH. Benzo[*a*]pyrene regulates osteoblast proliferation through an estrogen receptor-related cyclooxygenase-2 pathway. *Chem Res Toxicol*. 2004;17(5): 679–684.
42. Safe S, Wormke M. Inhibitory aryl hydrocarbon receptor-estrogen receptor alpha cross-talk and mechanisms of action. *Chem Res Toxicol*. 2003;16(7):807–816.
43. Rundle A, Tang D, Hibshoosh H, et al. The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. *Carcinogenesis*. 2000;21(7): 1281–1289.
44. Jebb SA, Cole TJ, Doman D, et al. Evaluation of the novel Tanita body-fat analyser to measure body composition by comparison with a four-compartment model. *Br J Nutr*. 2000;83(2):115–122.

45. Pietrobelli A, Rubiano F, St-Onge MP, et al. New bioimpedance analysis system: improved phenotyping with whole-body analysis. *Eur J Clin Nutr.* 2004;58(11):1479–1484.
46. Xie X, Kolthoff N, Bärenholt O, et al. Validation of a leg-to-leg bioimpedance analysis system in assessing body composition in postmenopausal women. *Int J Obes Relat Metab Disord*. 1999;23(10):1079–1084.
47. Nuñez C, Gallagher D, Visser M, et al. Bioimpedance analysis: evaluation of leg-to-leg system based on pressure contact footpad electrodes. *Med Sci Sports Exerc*. 1997;29(4): 524–531.
48. Cable A, Nieman DC, Austin M, et al. Validity of leg-to-leg bioelectrical impedance measurement in males. *J Sports Med Phys Fitness*. 2001;41(3):411–444.

The Shale Tipping Point:

The Relationship of Drilling to Crime, Traffic Fatalities, STDs, and Rents in Pennsylvania, West Virginia, and Ohio

Unabridged Version

Multi-State Shale Research Collaborative
December 2014

See http://www.multistateshale.org/shale-tipping-point for an abridged version of this report and http://keystoneresearch.org/MSSRC/tech_app for the online technical appendix.

About the Authors

Mark Price, Keystone Research Center's Labor Economist, holds a Ph.D. in economics from the University of Utah.
Stephen Herzenberg, KRC's Executive Director, holds a Ph.D. in economics from MIT.
Diana Polson, research and project consultant at the Keystone Research Center, holds a Ph.D. in political science from CUNY Graduate Center.
Sharon Ward, Director of the Pennsylvania Budget and Policy Center, received her BA from the State University of New York at Albany, and studied at the Rockefeller Institute of Public Policy and the Fells Institute of Government.
Ellis Wazeter was a summer intern with the Keystone Research Center. He is a freshman pursuing a BS in industrial and labor relations at Cornell University.
Luis E. Basurto was the 2014 Economic Analysis Research Network intern with the Keystone Research Center. He is pursuing a BBA in economics and finance with a minor in applied math at the University of Texas – Pan American.

Acknowledgements

This project is supported through grants from the Heinz Endowments, Stoneman Family Foundation, Hillsdale Foundation and Park Foundation. The Multi-State Shale Research Collaborative wishes to thank its funders for their ongoing support. Thanks to Frank Mauro and Michele Mattingly of the Fiscal Policy Institute in New York for their helpful comments. Thanks to Ellen Lyon, Keystone Research Center Communications Director and its Pennsylvania Budget and Policy Center (PBPC), for editorial assistance and guidance, and to Stephanie Frank, KRC Office Manager, for laying out the report and producing the charts and figures.

Table of Contents

Executive Summary

How does hydro-fracking affect the rural communities at the epicenter of drilling activity? A rich body of literature on the human impacts and lore exists from the Mountain West: of boomtowns and bar fights, and rising rents and rising crime that accompanied oil and gas development in Wyoming and Colorado in the 1980s and 1990s, and more recently in North Dakota shale oil fields.

Considerable evidence indicates that shale development has followed a similar trajectory in Pennsylvania. Work from academic researchers and advocacy groups such as Food and Water Watch, and our own in-depth examination of two high-intensity Pennsylvania drilling counties (Greene and Tioga) document increased traffic, damaged roads, rising rents, and intensified demands on police and local first responders.

These impacts are in addition to the growing environmental and public health impacts associated with hydro-fracking, from greater incidence of childhood asthma in Texas, to water contamination in Pennsylvania, to seismic activity in Ohio and Oklahoma.

In many states, regulation of drilling activity is controlled by state officials, leaving local officials with few options except to manage the consequences. A better understanding of the nature and timing of likely impacts can help local governments and residents anticipate, plan for, or avoid the inevitable negative consequences of shale development.

In this report, the Multi-State Shale Research Collaborative examined potential shale-related impacts identified in our prior work and that of others to further identify impacts and determine at what point their effects became evident. We looked at three states: Pennsylvania, Ohio, and West Virginia, dividing drilling counties in those states into three groups based on the level of drilling activity in order to better understand the relationship between the density of drilling and the severity of impacts. We used non-drilling rural and non-drilling urban counties as control groups, in order to account for relevant factors unrelated to shale development. Our analysis found impacts on housing, crime, traffic fatalities, and sexually transmitted diseases in communities with high levels of drilling. Although the impact of drilling is often localized within counties, data limitations necessitate use of county-level data (and, in the case of housing, multi-county data). As a result of this incongruity between the geography of drilling's impact and publicly available data sources, the impacts on crime, sexually transmitted diseases, traffic fatalities, and rents are likely to be underestimated.

Based on our analysis, we hypothesize that significant impacts emerge when the number of wells drilled in a given county exceeds 400 within a period of five to eight years.

Our main findings follow.

Drilling, Employment, and Population Trends

County Drilling Trends

Shale development is not evenly distributed across the states, nor across counties. Whether we see broad-based impacts depends on the level and concentration of drilling. Our analysis covered the 210 counties in

Pennsylvania, Ohio, and West Virginia. We divided these counties into five groups: low-, moderate--, and high-drilling counties; non-drilling rural counties; and non-drilling urban counties.

- Six Pennsylvania counties with more than 400 wells drilled were classified as high-drilling: Bradford, Tioga, Washington, Lycoming, Susquehanna, and Greene. As a group, they account for 52% of, or 4,515 of 8,634, new shale oil and gas wells drilled in Pennsylvania, West Virginia, and Ohio between 2005 and 2012.
- Ten West Virginia counties, one Ohio county, and six Pennsylvania counties, each with between 100 and 399 wells, were designated moderate-drilling counties. The 10 West Virginia counties account for 67% of the state's total shale oil and gas wells drilled between 2005 and 2012 (Kanawha, Logan, Ritchie, Harrison Doddridge, Boone, Upshur, Jackson, Wetzel, and Lincoln). Carroll County is the only Ohio county having more than 100 wells drilled; by 2013, 49% of all the unconventional wells in Ohio were located in Carroll County. Across all three states, the 17 moderate--drilling counties account for 30% of wells drilled from 2005 to 2012.

Employment

Consistent with our prior research (Mauro et al, 2013), we found modest employment growth in Pennsylvania, West Virginia, and Ohio from 2005 to 2012, particularly when measured as a share of total employment.

The bulk of employment impacts were found in the six high-drilling counties, where mining and natural resources employment rose by 138% (7,121 jobs) from 2005 to 2012 (compared to a decline of 2% from 1998 to 2005), and total employment across all industries grew by 10.3% (or 18,932 jobs).

In the remaining moderate- and low-drilling counties we found no statistically significant impact on total covered employment from drilling. In moderate-activity counties, mining and natural resources employment grew by 8% (1,126 jobs). Total employment actually declined in these counties, driven by a 1% total employment decline in moderate-drilling West Virginia counties that outweighed a 0.3% total employment increase in moderate-drilling Pennsylvania counties and a 6.4% employment growth in the one moderate-drilling Ohio county.. Carroll County employment trends and recent drilling activity are more similar to the six Pennsylvania high-drilling counties than to other moderate-drilling counties. In all three states, as a result of the Great Recession, total employment was down from 2005 to 2012 in both rural and urban non-drilling counties.

Population

We found little evidence in our data of significant population growth resulting from drilling.

The six high-drilling counties had a small population increase of 0.4%, or 2,040 people, between 2005 and 2012, reversing a small (0.3%) population decline during the prior seven-year period. The moderate-drilling counties in all three states have experienced a small decline in population since 2005 (0.9% in PA, 0.3% in WV, and 1.8% in OH). By contrast, since 2005, the population in non-drilling urban and

rural counties in all three states actually grew by about 3%.[1] Across county-level population data for West Virginia, Pennsylvania, and Ohio, we found that drilling did not have a positive and statistically significant impact on population growth for any grouping, including high-drilling counties.

Social and human impacts

Given the drilling, employment, and population trends described above, we would expect to observe social and human impacts (crime, traffic fatalities, sexually transmitted disease and rising rents) in high-drilling counties. In fact, across the counties studies, significant increases in the rates of crime, sexually transmitted diseases, motor vehicle fatalities, and increased housing costs were almost exclusively limited to the six high-drilling Pennsylvania counties.

Crime

- Violent crime
    - There was a statistically significant increase in violent crime of 17.7% in high-drilling counties; this increase corresponds to about 130 more violent crimes in these six counties in 2012. During this same period, the violent crime rate was down in both urban and rural non-drilling communities.
    - In moderate-drilling counties in Pennsylvania, West Virginia, and Ohio, we did not observe any statistically significant increases in violent crime or property crime over the period of this study. Carroll County, Ohio, which experienced a rapid increase in drilling only in the final year of this study (2012), will, if drilling continues apace, provide an important test of whether the increased crime rates observed in high-drilling counties in Pennsylvania also occur in other states with similar levels of drilling.

- Property Crime
    - We observed a statistically significant increase in property crime of 10.8% in high-drilling counties.
    - For the most part, we did not observe a statistically significant increase in violent crime and property crime in moderate- and low-drilling counties in West Virginia, Pennsylvania, and Ohio.[2]

- Drug and alcohol crime
    - Between 2005 and 2012, drug abuse rates rose 48% in the high-drilling counties in Pennsylvania, representing an annual increase of about 600 cases. In these same counties, DUI offenses were up 65%, compared to 42% in non-drilling rural areas, and little or no increase elsewhere across the state. The gap between the 65% and 42% increases amounts to an additional 400 cases per year across the six high-drilling counties.

[1] Some population trends in drilling areas led us to wonder whether year-to-year population statistics fully capture all of the out-of-state influx of people triggered by drilling, some of which could be temporary. Since our 2005-12 period includes data from the 2010 Census, it is unlikely that our drilling-area population estimates are substantially undercounted, but we are nonetheless consulting further with state demographers.

[2] We did, however, observe a statistically significant increase in violent crime in low-drilling counties.

Interestingly, drug abuse and DUI offenses did not increase substantially, and in some cases fell, in moderate- and low-drilling counties.

Sexually Transmitted Diseases

- Between 2005 and 2012, there was a statistically significant increase of 24% to 27% in rates of infection for chlamydia across all drilling counties (high-, moderate-, and low-) across all three states. There also was an increase in gonorrhea infection rates across all counties, but it was no higher in drilling counties than in non-drilling ones.

Motor Vehicle Fatalities

- There was a statistically significant increase of 27.8% in truck-involved motor vehicle fatalities in the high- drilling counties. In terms of all traffic fatalities (not just those involving trucks) Pennsylvania's six high-drilling counties also had about 35 more traffic fatalities in 2012 than if the number had followed the statewide trend. However this increase in overall motor vehicle fatalities between 2005 and 2012 was not statistically significant.
- We observed no increase in motor vehicle fatalities overall or in truck-involved fatalities in moderate-drilling counties in West Virginia, Pennsylvania, and Ohio.[3]

Rental Housing Markets[4]

Some of the most widely reported impacts of shale oil and gas development relate to housing shortages and rapidly rising rents.

- In high-drilling counties, we observed statistically significant increases in median, low (20th percentile) and high (80th percentile) rents of 10.2%, 7.6% and 12.3%, respectively. We observed no statistically significant impacts for moderate- or low-drilling counties.
- There is a clear pattern of rising rents in the middle and near the top (80th percentile) of the rental market in high-drilling areas.
    - Median rents rose by the indicated rates in the following groups of Pennsylvania counties (***bold italics*** denote heavy-drilling counties): 16.5% in ***Bradford***, Sullivan & ***Tioga***; 9.4% in ***Greene*** and ***Washington***; and 13.9% in Pike, ***Susquehanna***, and Wayne.
- In Ohio, low and median rents were up 3.2% and 1.7%, respectively, in ***Carroll County*** (112 wells drilled) and Stark County (7 wells drilled).

With respect to changes in the incomes of renters, in high-drilling counties we observed a statistically significant increase in renter incomes only at the 80th percentile. By contrast, in medium- and low-drilling counties we observed declines in the incomes of renters at the 20th percentile. With rising rents and no change in incomes for low- (20th percentile) and median- income renters in high-drilling counties, there was a statistically significant 14% increase in the number of renters paying 30% or more of their income in rent (a measure of housing affordability). It is also of note that, although there were rising median and

[3] We did observe a decline of 11% in low-drilling counties in motor vehicle fatalities overall.
[4] Note that we are hampered in this analysis by having to rely on data for "county groups" rather than individual counties. Grouping heavy-drilling Bradford, Tioga, and Greene counties with other counties likely masks bigger impacts of drilling on housing variables in those individual counties.

high rents in high-drilling counties, we found no evidence of an increase in new residential housing construction over the 2005-2012 period.

Conclusion

One challenge for the future is to improve data sources to get a better match between the area where drilling is occurring and the information available on human and social service impacts.

What do we know from analyzing the data that are currently available as well as our prior case studies? Summing up, our case studies of two high-drilling Pennsylvania counties, Tioga and especially Greene, revealed some positive employment and income benefits of shale development. Our assessment of the human and social impacts in this report reveals the other side of this positive-economic impacts coin: The heaviest drilling counties, as measured by number of wells and by industry and total employment impacts, also experience negative impacts. These include higher rates of crime, sexually transmitted disease, and traffic fatalities, and higher rents.

In a sense, these findings echo the old saying that “there’s no free lunch.” The communities in which the scale of shale development is sufficient to move the needle on total employment and income are also the communities likely to be faced with social challenges. Communities with shale resources where drilling has not yet occurred should understand this trade-off so that they may weigh their options in an informed way and prepare for the social impacts if drilling is undertaken.

Introduction

Unconventional shale oil and gas extraction is a high-impact industrial process, especially when considered relative to conventional oil and gas extraction, which has been present in Pennsylvania, Ohio, and West Virginia since the discovery of oil in the 19th century. Some economic and social impacts of shale development result directly from drilling itself, e.g., traffic- and road-related impacts. Other impacts result from an influx of people and income directly or indirectly associated with industry development, such as increases in crime, sexually transmitted diseases and housing costs. Because we anticipate that drilling-related social impacts are associated with the amount of drilling and with changes in industry employment, total employment, and population, we begin our analysis in Chapter 1 with a summary of county-level trends in the number of wells drilled, total employment, and population trends in each state.

Based on this analysis, we find that six Pennsylvania counties— each with more than 400 wells drilled—stand far above all the others studied for the amount of drilling and also for industry employment growth. We define these as high-drilling counties. No county in Ohio has had more than 112 wells drilled, and no county in West Virginia has had more than 200 wells drilled. To permit analysis of drilling's human service impacts in all three states, we created a second group of medium-drilling counties with between 100 and 399 wells drilled. In addition to these two categories, we also look in subsequent chapters for drilling impacts in counties with 1 to 99 wells (low-drilling) and in two control groups, rural counties without drilling and urban counties without drilling.[5]

Map 1.1, Map 1.2, and Map 1.3 in Chapter 1 identify the counties that fall into each of these categories in Pennsylvania, West Virginia, and Ohio. When possible, we examine trends in our social and economic variables prior to drilling and also present trends in these same variables in the non-drilling rural and urban portions of New York, Maryland, and Virginia.

Using these groupings, we explore in each state whether the counties with the most drilling have seen changes in job growth (Chapter 2) and population (Chapter 3) above and beyond that found in control areas.[6]

In the remaining chapters we explore trends in crime (Chapter 4), sexually transmitted diseases (Chapter 5), and traffic fatalities (Chapter 6).

In Chapter 7 we examine trends in rents, renter income, rental housing affordability, home values, and homeowner incomes. Data limitations imposed by our use of the American Community Survey for these analyses mean that observations from high-drilling counties are pooled with those from counties much less drilling, likely resulting in the underestimation of the impact of heavy drilling.

[5] Whenever possible in the subsequent chapters we also present trends in the rural and urban portions of New York, Virginia, and Maryland. These are the other states in the region that may have shale oil and gas.
[6] In an Online Technical Appendix we also present county-by-county trends in each of the areas we study for counties with 100 or more wells drilled.

In Chapter 8 we expand our analysis to four additional potential human service impact areas: early intervention for children with developmental delays or disabilities, foster care, and emergency room visits. Since data in these areas are not uniform across states, we restrict our analysis to Pennsylvania, the state with the most drilling over the period studied.

Box 1. Online Technical Appendix

Find online at http://keystoneresearch.org/MSSRC/tech_app Excel files of the tables printed in this document, as well as supplementary tables with individual county-level outcomes for each of the topics covered in this report.

Researchers interested in exploring the strength of the relationships between drilling intensity and the topics covered in this report can also find here Stata datasets containing the variables summarized in this study.

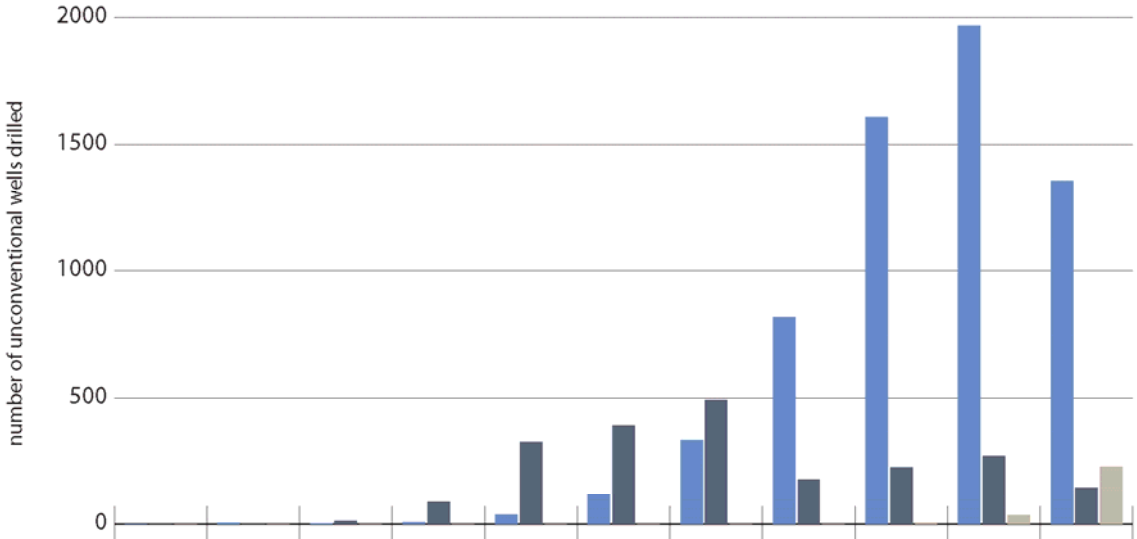
Chapter 1: State and County Trends in Drilling

To better understand the human and social impacts of drilling in Pennsylvania, West Virginia and Ohio, we need to explore where and when that drilling created changes in employment and population.

We start the process by looking at the timeline of drilling at the state level—the number of wells drilled each year in our three states (Figure 1.1). Three points stand out from this figure. First, Pennsylvania accounts for much more drilling than West Virginia and Ohio, with 72% of total wells drilled across all three states from 2005 to 2012. Second, drilling started in earnest first in West Virginia, peaking in 2008 at only one quarter the peak drilling level in Pennsylvania. Third, drilling in Ohio does not begin until 2011, and only exceeds 35 wells in 2012, the final year of this study.

Figure 1.1

Number of Unconventional Wells Drilled By Year in Pennsylvania, West Virginia, and Ohio



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Pennsylvania	1	4	2	8	37	115	335	817	1607	1968	1358
West Virginia	0	0	12	89	326	392	492	178	227	270	146
Ohio	0	0	0	0	1	0	0	1	4	35	229

Source. Multi-State Shale Collaborative based on Pennsylvania Department of Environmental Protection (DEP), the West Virginia Geological and Economic Survey (WVGES), and the Ohio Department of Natural Resources (DNR).

Table 1.1 examines the amount of drilling by county for all counties in the three states with at least 100 wells drilled from 2005 to 2012. This table reveals that the top six Pennsylvania drilling counties, each with at least 517 wells drilled, had more than two-and-a-half times as many wells drilled as any West Virginia county and nearly five times as many as any Ohio county. These six counties accounted for more than half (52%) of all wells drilled in the three states from 2005 to 2012. The table further reveals that the top two counties for total wells drilled (Bradford and Tioga in Pennsylvania) are also the top two counties for wells drilled per capita. The fifth- and sixth-ranked counties for wells drilled (Susquehanna and Greene in Pennsylvania) also ranked fifth and sixth for wells drilled per capita. The third- and fourth-

place counties for wells drilled (Washington and Lycoming in Pennsylvania) are more urban and therefore rank lower for wells drilled per capita. Meanwhile, the third- and fourth-place counties measured by wells drilled per capita are sparsely populated Doddridge and Ritchie in West Virginia, with only 16 and 12 wells drilled over the 2005-2012 period, respectively. In sum, based on drilling intensity alone, we should expect to see human and social service impacts in the top six Pennsylvania drilling counties, and especially in the four less populous of those counties because they rank in the top six BOTH for total number of wells drilled and for wells drilled per capita.

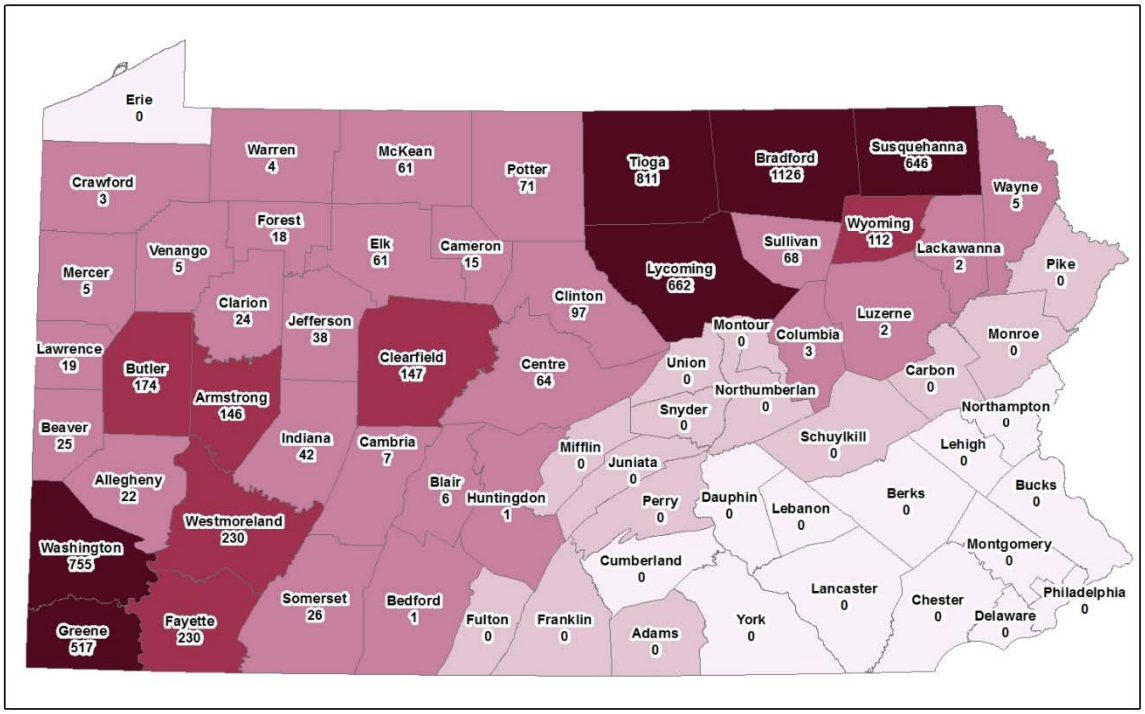
Table 1.1

The amount of drilling activity by county in Pennsylvania, West Virginia, and Ohio counties with at least 100 wells drilled from 2005 to 2012

State	county	total wells drilled	total wells drilled rank	wells drilled per capita	wells drilled per capita rank
Pennsylvania	Bradford	1126	1	0.018	2
Pennsylvania	Tioga	811	2	0.019	1
Pennsylvania	Washington	755	3	0.004	16
Pennsylvania	Lycoming	662	4	0.006	8
Pennsylvania	Susquehanna	646	5	0.015	5
Pennsylvania	Greene	517	6	0.014	6
Pennsylvania	Fayette	230	7	0.002	20
Pennsylvania	Westmoreland	230	8	0.001	23
West Virginia	Kanawha	194	9	0.001	21
West Virginia	Logan	191	10	0.005	9
Pennsylvania	Butler	174	11	0.001	22
West Virginia	Ritchie	163	12	0.016	4
West Virginia	Harrison	156	13	0.002	17
Pennsylvania	Clearfield	147	14	0.002	19
Pennsylvania	Armstrong	146	15	0.002	18
West Virginia	Doddridge	137	16	0.017	3
West Virginia	Boone	122	17	0.005	12
West Virginia	Upshur	122	18	0.005	11
West Virginia	Jackson	121	19	0.004	13
West Virginia	Wetzel	115	20	0.007	7
Ohio	Carroll	112	21	0.004	15
Pennsylvania	Wyoming	112	22	0.004	14
West Virginia	Lincoln	111	23	0.005	10

Source. Multi-State Shale Collaborative based on Ohio Department of Natural Resources, Pennsylvania Department of Environmental Protection, West Virginia Geological and Economic Survey, and Bureau of Economic Analysis data.

Map 1.1



Source. Multi-State Shale Collaborative.

Table 1.2

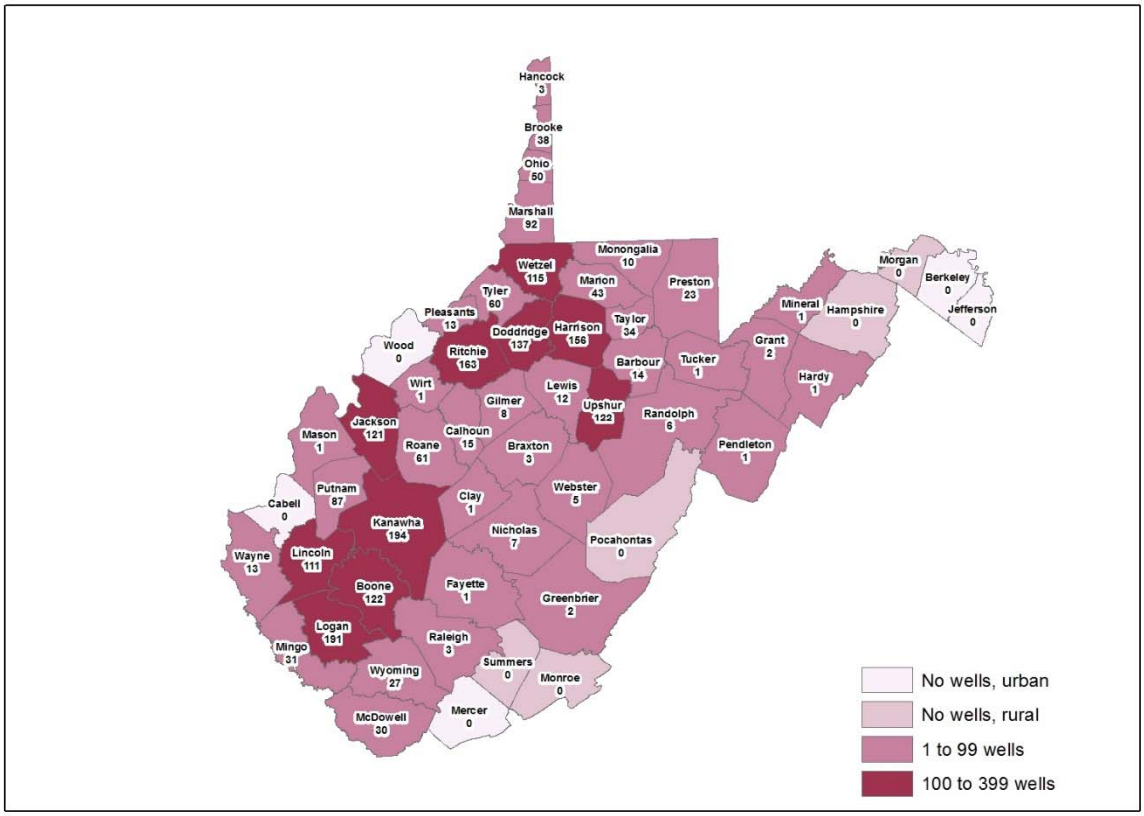
Share of total wells drilled each year for the top six drilling counties in Pennsylvania

Year	Pennsylvania (Number of Wells Drilled)	Brad-ford	Tioga	Wash-ington	Lycom-ing	Susque-hanna	Greene	Six county share of PA total
2002	1	0%	0%	100%	0%	0%	0%	100%
2003	4	0%	0%	25%	0%	0%	0%	25%
2004	2	0%	0%	0%	0%	0%	0%	0%
2005	8	13%	0%	63%	0%	0%	0%	75%
2006	37	5%	3%	51%	0%	3%	5%	68%
2007	115	2%	0%	39%	4%	2%	12%	59%
2008	335	7%	4%	20%	4%	10%	20%	65%
2009	817	19%	15%	12%	3%	11%	12%	73%
2010	1607	23%	17%	10%	7%	8%	6%	73%
2011	1968	20%	14%	8%	15%	10%	6%	74%
2012	1358	12%	9%	14%	15%	14%	8%	72%
Total wells drilled	6252	18%	13%	12%	11%	10%	8%	72%

Source. Multi-State Shale Collaborative based on Pennsylvania Department of Environmental Protection (DEP) data.

In the six top-drilling counties, Table 1.2 shows the timeline of drilling. Drilling from 2006 to 2008 was concentrated in Washington and Greene counties in the southwest corner of Pennsylvania. Drilling then expanded rapidly in the four northeast Pennsylvania counties, Bradford, Tioga, Lycoming, and Susquehanna.

Map 1.2



Source. Multi-State Shale Collaborative

In West Virginia, the 10-top drilling counties composed 67% of the state's total unconventional drilling during the 2002-12 period (Map 1.2). Table 1.3 shows that the locus of drilling within West Virginia has shifted over time, from the southwest to the northwest (Doddridge, Harrison, Upshur, and Wetzel counties). Table 1.3 show that drilling dropped off by more than two-thirds from 2008 to 2012. Thus, based on the lack of sustained drilling intensity in any part of the state, there is a question whether West Virginia should expect significant human and social impacts from drilling.

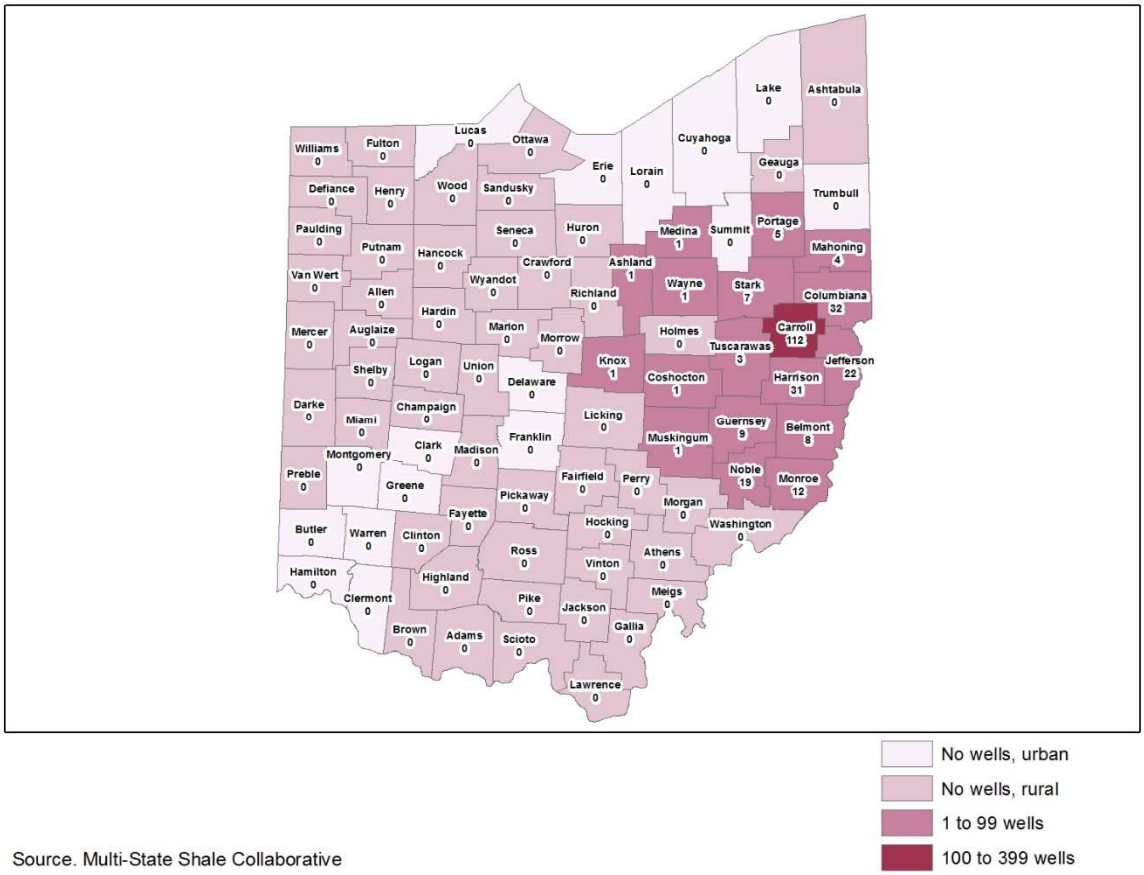
Table 1.3

Wells drilled as a share of total wells for the top ten drilling counties in West Virginia

County	year									Share of total since 2004
	2004	2005	2006	2007	2008	2009	2010	2011	2012	
Kanawha	17%	6%	18%	11%	15%	4%	0%	0%	0%	9%
Logan	0%	37%	18%	19%	5%	0%	0%	0%	0%	9%
Ritchie	0%	4%	13%	15%	7%	3%	1%	3%	3%	8%
Harrison	0%	0%	0%	0%	3%	8%	17%	19%	22%	7%
Doddridge	0%	0%	0%	0%	7%	19%	21%	1%	12%	6%
Boone	25%	13%	13%	8%	5%	0%	1%	0%	0%	6%
Upshur	0%	0%	0%	2%	3%	10%	19%	11%	5%	6%
Jackson	0%	4%	1%	13%	10%	4%	2%	0%	0%	6%
Wetzel	0%	0%	0%	1%	3%	18%	12%	8%	10%	5%
Lincoln	0%	0%	12%	8%	8%	3%	0%	0%	0%	5%
statewide total	12	89	326	392	492	178	227	270	146	2132

Source. Multi-State Shale Collaborative based on the West Virginia Geological and Economic Survey (WVGES) data.

Map 1.3



Source. Multi-State Shale Collaborative

Significant drilling started in Ohio in 2011, with 35 new wells, and then jumped to 229 new wells in 2012. That was 83 more wells than were drilled in West Virginia that same year but only about one-sixth the number of wells drilled in Pennsylvania in 2012. Drilling in Ohio, so far, is concentrated near the eastern border with West Virginia, with only one county (Carroll) having more than 100 wells drilled (See Table 1.4 and Map 1.3). Carroll County had more wells drilled in 2010 (94 wells) than any one West Virginia county has had drilled in a single year. Within all three states from 2005 to 2012, Carroll County's drilling activity in 2012 has only been exceeded in any single year by the six Pennsylvania high-drilling counties.

Table 1.4

Wells drilled in Ohio and Carroll County, Ohio

Year	Ohio total	Carroll
2006	1	0%
2007	0	0%
2008	0	0%
2009	1	0%
2010	4	0%
2011	35	51%
2012	229	41%
Total Wells Drilled	270	41%

Source. Multi-State Shale Collaborative based on the Ohio Department of Natural Resources (DNR).

Chapter 2: Job Growth

Next we consider whether drilling in individual counties translated into an impact on jobs and population. We know from our prior research that across ALL drilling counties, the relationship between drilling and employment is a weak one (Mauro et al 2013). For the heaviest drilling counties, however, this relationship could be stronger. For example, the Census Bureau (2013) finds the fastest growing communities in the country are those undergoing energy natural resource extraction booms.

In examining employment and population (discussed in detail next chapter) trends, we compare changes in the seven-year period after drilling picked up (2005-2012) with a seven-year period ending in 2005 (1998-2005) (see Table 2.1). The period from 1998 to 2005, including the 2001 recession, measures employment change roughly from peak to peak of the business cycle. The period from 2005 to 2012 includes the Great Recession and ends in a year when employment remained closer to the trough of the business cycle. Thus, unless shale-specific factors (or other local factors) outweigh the impact of the national economy, we would expect total employment gains from 1998 to 2005 but flat or declining employment from 2005 to 2012.[7]

Table 2.1 shows changes in industry employment, total employment, and population in each of the counties with at least 100 wells drilled across all three states. (We measure industry employment using "mining and natural resources employment" because narrower industry definitions are not available for all counties[8]). Four of the Pennsylvania high-activity drilling counties have industry employment increases of over a 1,000 jobs (three have increases of over 1,700 jobs); a fifth high-activity county, Tioga, also has a big mining and natural resources employment increase in percentage terms (376%). Only one county outside the "big six" has an industry employment increase of over 300% —Carroll County in Ohio.[9]

Tables 2.2 and 2.3 show industry (natural resources and mining) and total employment changes for our county groups, starting with the six Pennsylvania counties with 400 or more wells drilled (what we previously defined as high-activity). Table 2.2 shows that the high activity Pennsylvania counties saw industry employment increases of 138%, over two-and-a-half times greater than any other grouping except for Carroll County (in a group by itself). These six counties also saw an increase in employment between 2005 and 2012 of 10.3% (or 18,932 jobs), while both rural and urban Pennsylvania counties without drilling saw employment decline by 1.5% and 0.8%, respectively. Washington and Greene counties together account for 13,579 (71%) of the job gains in the high-drilling counties. As discussed in Chapter 1, these two southwestern counties accounted for a third of the wells drilled in Pennsylvania since 2005. Thus, total employment gains in Greene and Washington appear to reflect growth in both

[7] For the purposes of this paper, we will briefly focus on changes in total covered employment (hereafter referred to as employment) as measured in the Quarterly Census of Employment and Wages between 1998 and 2012.
[8] The use of this broader definition means that in some counties trends in non-shale employment, including coal mining, may drive the numbers. This may particularly impact Greene and Fayette counties in Pennsylvania and some West Virginia counties.
[9] With 93 new jobs, an increase of 291% in Wetzel County, West Virginia, just misses the 300% cutoff.

drilling and non-drilling sectors.[10] In the remaining top-six drilling counties, employment gains were modest, ranging from 4% to 8%.

Table 2.2

Mining and natural resources employment change from 1998 to 2012 in counties grouped by the amount of drilling

Wells drilled/region	Employment 2012	1998 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent Change	Change	Percent Change	
PA, 400 or more wells	12,284	-108	-2%	7,121	138%	4,515
PA, 100 to 399 wells	5,298	-499	-10%	971	22%	1,036
PA, 1 to 99 wells	15,632	-200	-2%	5,442	53%	693
PA, Rural*	5,158	-48	-1%	482	10%	0
PA, Urban*	16,098	2,540	17%	-1,184	-7%	0
WV, 100 to 399 wells	10,094	1,869	23%	21	0.2%	1,427
WV, 1 to 99 wells	20,704	-115	-1%	5,978	41%	693
WV, Rural*	115	-80	-34%	-40	-26%	0
WV, Urban*	736	-91	-12%	74	11%	0
OH, 100 to 399 wells (Carroll, OH)	173	-46	-54%	134	344%	112
OH, 1 to 99 wells	7,210	439	7%	694	11%	158
OH, Rural*	9,359	-1,825	-17%	148	2%	0
OH, Urban*	6,197	-815	-11%	-508	-8%	0
MD, Rural*	3,711	248	7%	116	3%	0
MD, Urban*	1,861	241	13%	-169	-8%	0
NY, Rural~	19,410	2,573	17%	1,250	7%	21
NY, Urban*	7,736	-80	-1%	-84	-1%	0
VA, Rural~	17,148	-1,901	-10%	-40	-0.2%	93
VA, Urban*	2,972	-27	-1%	-338	-10%	0

*The figures here represent employment in rural and urban counties with no wells drilled between 2002 and 2012. A county or county group is defined as rural if the 2005 population per square mile is below its corresponding statewide total population per square mile. What follows is the population per square mile for each state in this study: Pennsylvania (278); West Virginia (75); Maryland (576); New York (405); Ohio (280); Virginia (191).

~ There were 93 wells drilled in rural Virginia counties and 22 wells drilled in rural New York counties between 2002 and 2012.

Source. Multi-State Shale Collaborative based on Quarterly Census of Employment and Wages data.

[10] For instance, in this period coal production was increasing in Greene County, and casino gaming was expanding in Washington County.

Table 2.3

Employment change 1998 to 2012 in counties grouped by the amount of drilling.

Wells drilled/region	Employment 2012	1998 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent Change	Change	Percent Change	
PA, 400 or more wells	202,596	9,489	5.4%	18,932	10.3%	4,515
PA, 100 to 399 wells	314,582	21,437	7.3%	997	0.3%	1,036
PA, 1 to 99 wells	1,507,614	6,510	0.4%	-11,284	-0.7%	693
PA, Rural*	328,950	30,027	9.9%	-5,035	-1.5%	0
PA, Urban*	3,096,180	123,344	4.1%	-25,371	-0.8%	0
WV, 100 to 399 wells	187,367	-494	-0.3%	-1,898	-1.0%	1,427
WV, 1 to 99 wells	329,723	12,379	4.0%	10,242	3.2%	693
WV, Rural*	14,171	494	3.4%	-955	-6.3%	0
WV, Urban*	156,232	3,678	2.4%	-306	-0.2%	0
OH, 100 to 399 wells (Carroll, OH)	5,950	-871	-13.5%	359	6.4%	112
OH, 1 to 99 wells	617,112	-6,987	-1.0%	-45,585	-6.9%	158
OH, Rural*	1,017,375	7,749	0.7%	-71,910	-6.6%	0
OH, Urban*	3,321,113	-25,367	-0.7%	-187,080	-5.3%	0
MD, Rural*	608,634	98,081	19.6%	9,390	1.6%	0
MD, Urban*	1,841,543	135,958	7.9%	-12,365	-0.7%	0
NY, Rural~	1,368,950	65,329	4.9%	-30,245	-2.2%	21
NY, Urban*	7,053,753	196,580	3.0%	235,857	3.5%	0
VA, Rural~	806,703	41,373	5.2%	-25,261	-3.0%	93
VA, Urban*	2,738,630	301,631	12.7%	52,700	2.0%	0

*The figures here represent employment in rural and urban counties with no wells drilled between 2002 and 2012. A county or county group is defined as rural if the 2005 population per square mile is below its corresponding statewide total population per square mile. What follows is the population per square mile for each state in this study: Pennsylvania (278); West Virginia (75); Maryland (576); New York (405); Ohio (280); Virginia (191).

~ There were 93 wells drilled in rural Virginia counties and 22 wells drilled in rural New York counties between 2002 and 2012.

Source. Multi-State Shale Collaborative based on Quarterly Census of Employment and Wages data

In West Virginia, drilling does not appear to have been extensive enough to drive overall employment trends. Counties with 100 to 399 wells (medium-activity), which account for 67% of the state's new unconventional oil and gas wells, experienced a decline in total employment of 1% since 2005 (Table 2.3). Counties with less drilling (between 1 and 99 wells or low-activity) saw employment climb 3.2%. In

rural West Virginia counties without drilling, employment fell 6.3%, and in urban West Virginia counties without drilling, it fell 0.2%.[11]

In Ohio, only Carroll County had more than 100 wells drilled (no other Ohio county had more than 32 wells drilled) between 2002 and 2012, with total employment growing by 6.4%, or 359 jobs, since 2005 (Table 2.3). The employment picture in the rest of Ohio was grim before and after 2005.

Panel regression on employment

Using our annual data set (1998 to 2012) of total covered employment and employment in mining and natural resources (expressed in logs), we estimated using a fixed effects panel regression the relationship between employment and the amount of drilling activity by county in West Virginia, Pennsylvania and Ohio. We included three indicator variables set to 1 for counties between 2005 and 2012 (the period in which drilling occurred) that also had high-activity (400 or more wells drilled over the period), medium-activity (100 to 399 wells drilled over the period) and low-activity(1 to 99 wells drilled over the period) and zero otherwise.[12] In terms of total covered employment, we found a positive and significant elasticity for high-activity counties, implying an increase in total covered employment of 10.5%. For medium-activity counties we failed to find a statistically significant coefficient. In low-activity counties the coefficient is negative and statistically significant. The relationship between drilling and employment in natural resources and mining is stronger across all counties with an elasticity ranging from .203 in low-activity counties to 1.085 in high-activity counties. Consistent with our prior work the only places to see significant employment impacts are those six high-activity counties in Pennsylvania.

[11] Some individual counties (Kanawha, Logan, and Harrison) did in relative terms have stronger employment growth since 2005 than prior (see the Online Technical Appendix, Appendix B, Table B1 for a county-by-county breakout of employment gains in each state with 100 or more wells drilled).

[12] As reflected in the absence of a full set of controls, our intent here is not to fully explain differences in employment across counties but to assess the relationship between drilling and employment. Researchers interested in exploring the robustness of this relationship can find this dataset in the Online Technical Appendix, Chapter 2, AppendixB.dta (stata).

Table 2.4

Employment in West Virginia, Pennsylvania and Ohio by high-, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of total covered employment	Dependent variable = natural log of natural resources and mining employment
	b/se	b/se
High-activity	0.105***	1.085***
	(0.026)	(0.209)
Medium-activity	0.016	0.322**
	(0.014)	(0.130)
Low-activity	-0.017**	0.203***
	(0.008)	(0.046)
Constant	9.879***	5.623***
	(0.000)	(0.001)
R-sqr-overall	0.001	0.011
N	3,149	2,688

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels. Standard error estimates are robust to disturbances being heteroscedastic.

Chapter 3: Population

We now turn to population. As a group high-activity counties (those with 400 or more wells) in Pennsylvania saw their population increase by 0.4%, or 2,040 people, after 2005, whereas prior to 2005 these same counties experienced a population decline of 0.3%.[13] (Recall that Table 2.1 had individual county population changes for counties with 100 or more wells drilled). Since 2005, the population in urban and rural Pennsylvania counties without drilling grew by 4.4% and 3.4%, respectively. (See the Online Technical Appendix, Chapter 3, Table C1 for a county-by-county breakout of population trends in counties with 100 or more wells drilled).[14]

Considered as a group, the heaviest drilling counties in West Virginia, those with between 100 and 399 wells (medium-activity), experienced a decline in population since 2005 of 1,365 people, or 0.3%, compared to a decline of 2.9% from 1998 to 2005.[15] In comparison, urban and rural West Virginia counties without drilling grew by 6.3% and 2.6%, respectively. In Carroll County, Ohio, despite recent gains in total employment, the county population is down by 531 people, or 1.8%, since 2005.[16]

Using data from the 2000 Census and the 2008-2012 American Community Survey, we also examined the population share of males ages 15 to 39 by county in West Virginia, Pennsylvania and Ohio. Reflecting broader demographic trends, the share of males ages 15 to 39 fell across all three states, and we could identify no clear pattern by the level of drilling activity. (See the Online Technical Appendix, Chapter 3, Table C2 and Table C3, for a county-by-county breakout of the change in the share of males ages 15 to 39 in counties with 100 or more wells drilled).

We interviewed demographers at the Penn State Data Center who acknowledged that local officials in drilling communities in Pennsylvania expressed some concern that the 2010 Census did not confirm as much population growth as they were expecting, given reports of increasing rents and shortages of local hotel rooms. To the extent that drillers use out-of-state workers, those workers may not necessarily report that they reside in the states studied here. Thus these workers would not show up in the population data summarized here. Similarly, a sizable share of employment generated by drilling is in the construction sector where it is in the nature of the industry for workers to travel long distances to find work, and this is especially true in rural regions.

[13] As a group, these Pennsylvania counties account for 72% of the 6,245 wells drilled in Pennsylvania since 2005.
[14] See Table C4 in Chapter 3 of the Online Technical Appendix for the results of a fixed-effects panel regression on population (expressed in logs) by county from 1998 to 2012 in West Virginia, Pennsylvania and Ohio. The model included no other independent variables than three indicator variables set to 1 for every year from 2005 to 2012 in high-activity counties (those with 400 or more wells), medium-activity counties(100 to 399 wells), and low-activity counties (1 to 99 wells) and 0 otherwise. None of the coefficients on the indicator variables were statistically significant for any level of drilling. If there were population impacts from drilling they were too small to be detectable in county-level population data.
[15] As a group, these West Virginia counties account for 67% of that state's 2,120 unconventional oil and gas wells.
[16] The population in Carroll County in 2012 was down by 213 individuals compared to its 2010 level.

Table 3.1

Population change 1998 to 2012 by state and by number of wells drilled

Wells drilled/region	2012	1998 to 2005		2005 to 2012		Total wells drilled 2002 to 2012
		Change	Percent Change	Change	Percent Change	
PA, 400 or more Wells	512,034	-1,698	-0.3%	2,040	0.4%	4,515
PA, 100 to 399 Wells	861,743	-7,972	-0.9%	-7,750	-0.9%	1,036
PA, 1 to 99 Wells	3,362,037	-92,214	-2.7%	-12,135	-0.4%	693
PA, Rural*	1,020,081	64,707	7.0%	33,661	3.4%	0
PA, Urban*	7,007,641	241,495	3.7%	297,730	4.4%	0
WV, 100 to 399 Wells	432,140	-12,856	-2.9%	-1,365	-0.3%	1,427
WV, 1 to 99 Wells	938,401	-8,493	-0.9%	10,258	1.1%	693
WV, Rural*	77,072	4,457	6.3%	1,947	2.6%	0
WV, Urban*	407,800	21,775	6.0%	24,081	6.3%	0
OH, 100 to 399 Wells (Carroll, OH)	28,587	481	1.7%	-531	-1.8%	112
OH, 1 to 99 Wells	1,718,010	17,729	1.0%	-5,851	-0.3%	158
OH, Rural*	2,938,175	78,777	2.8%	16,503	0.6%	0
OH, Urban*	6,859,453	54,797	0.8%	70,784	1.0%	0
MD, Rural*	1,710,001	180,039	12.5%	87,855	5.4%	0
MD, Urban*	4,174,562	207,876	5.5%	204,329	5.1%	0
NY, Rural~	3,822,058	62,491	1.7%	10,026	0.3%	21
NY, Urban*	15,748,203	314,213	2.1%	427,625	2.8%	0
VA, Rural~	2,393,746	124,590	5.7%	86,762	3.8%	93
VA, Urban*	5,792,121	551,597	11.7%	522,000	9.9%	0

*The figures here represent employment in rural and urban counties with no wells drilled between 2002 and 2012.

~ There were 93 wells drilled in rural Virginia counties and 22 drilled in rural New York counties between 2002 and 2012.

Note. A county or county group is defined as rural if the 2005 population per square mile is below its corresponding statewide total population per square mile. What follows is the population per square mile for each state in this study: Pennsylvania (278); West Virginia (75); Maryland (576); New York (405); Ohio (280); Virginia (191).

Source. Multi-State Shale Collaborative based on Bureau of Economic Analysis data

Chapter 4: Crime

Natural resource extraction booms tend to lead to an influx of out-of-state workers, including transient young men making higher-than-average wages. With this influx and the extraction activity, traffic increases, local bars and restaurants fill up, and small town life changes. Numerous studies have found that this influx corresponds to an increase in crime and a greater demand on emergency services.

The Long-Term Link between Natural Resource Extraction and Crime:

In *Long-term effects of income specialization in oil and gas extraction: the U.S. West, 1980-2011*, researchers observed that counties in the American West that derive more of their income from oil and gas extraction for a longer period of time experienced higher violent and property crime rates than other counties in the region (page 13 bottom).

To read more: http://headwaterseconomics.org/wphw/wp-content/uploads/OilAndGasSpecialization_Manuscript_2013.pdf

Several studies have documented that rising crime accompanies unconventional gas booms. Murray and Ooms (2008) found increases in population and crime during the height of gas extraction in Denton city and Wise County, Texas, and in Faulkner and White counties, Arkansas. Similar trends were found in Sublette County, Wyoming, where increases in population led to rising crime and the need for more law enforcement. Another study of Sublette County documented that arrests grew faster than the population between 1995 and 2004 and showed links between the growth in gas drilling and the growth in the crime rates (Jacquet 2005).

Research in Sweetwater County, Wyoming, revealed a sharp increase in crime, which coincided with the boom in oil and gas extraction. The county saw a particularly high increase in drug-related arrests, which increased from 90 in 2002 to 450 in 2006 (Headwaters Economics 2009).

In Pennsylvania, the influx of well-paid young men who work in (or are connected to) the gas industry has led to reports of increases in drunk-driving, assaults, domestic disturbances and prostitution (Levy 2011). In Williston, North Dakota, there has been an increase in reported rape (about one complaint each week, most often of date rape, say local police). Police rarely got these types of complaints before the gas boom (Ellis 2011).

Case Study Findings

In the spring and summer of 2013 researchers from the Multi-State Shale Research Collaborative conducted interviews with local stakeholders in Tioga and Greene Counties, Pennsylvania; Wetzel County, West Virginia; and Carroll County, Ohio, to examine the social and human service impacts of gas drilling on these local communities.

In Greene County, Pennsylvania, arrests and calls to police increased during the height of the gas boom. The police in Cumberland Township, a center of heavy drilling, reported that calls doubled between 2008 and 2011, and arrests rose for driving under the influence (DUIs), theft, bar fights, assaults, and prostitution. Serious crime[17] rose in Greene County by 31% between 1999-2001 and 2010-12, while

[17] The Pennsylvania State Police include murder, forcible rape, robbery, aggravated assault, burglary, larceny, motor vehicle theft, and arson as serious crime.

Pennsylvania's crime rate fell by 6%. This increase was concentrated in two main areas—burglary and larceny. Escorting wide-load tractor-trailers and handling traffic-related accidents, including minor things like knocked over side mirrors and mailboxes, also increased demand on police (Herzenberg, Polson, and Price 2014).

In Tioga County, Pennsylvania, drilling was associated with increased crime and increased demands on emergency service personnel. Serious crime rose 13% in Tioga County between the period 1999-2000 and 2011-12, while across Pennsylvania serious crime declined by 6%. Tioga County's rise in crime was driven by increases in aggravated assault, larceny, burglary, and motor vehicle theft. DUIs increased 40% in Tioga compared to an increase of 28% statewide between 1999-2001 and 2010-12. Higher crime has meant higher costs to the county as the number of new criminal cases jumped 25% between 2010 and 2011 at the height of the gas boom.

Mansfield and Wellsboro, Tioga County's two population hubs, also saw calls to police and arrests increase with the gas boom. Between 2009 and 2011, calls to the Mansfield Police Department tripled. Wellsboro saw a spike in traffic and other citations. Misdemeanor arrests rose 82% from 2009 to 2011. One sexual assault victim resource organization in Tioga reported seeing rises in the number of sexual assaults (some with the use of date rape drugs) and women seeking domestic violence services during the height of the boom (Ward, Polson, Price 2014).

In Wetzel County, West Virginia, interviewees did not report increases in crime or 911 calls (although data below do show an increase in violent crime, property crime, and non-serious criminal offenses between 2009 and 2012). The Sherriff's office noted a slight increase in DUI arrests and an increase in traffic citations for speeding and driving left-of-center. County commissioners reported complaints from citizens about increased traffic and hazardous driving by trucking companies. (Corroborating this claim, vehicle accidents increased from 194 in 2007 to 310 in 2012 [O'Leary 2014]).

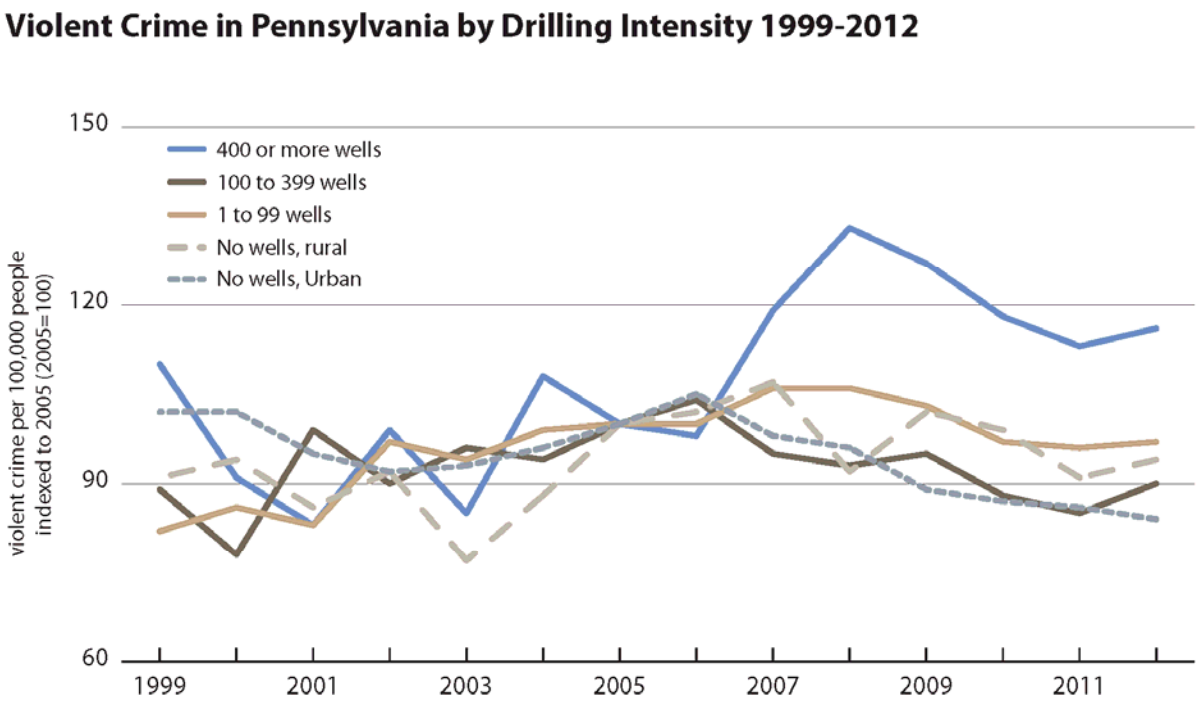
Interviewees in Ohio reported a quadrupling of calls to the sheriff between 2011 and 2013; those calls, plus a doubling of traffic accidents primarily involving heavy trucks, had reportedly increased the workload for the sheriff's office (Woodrum 2014).

Notes on Crime Data

In this chapter we used county-level crime data to more rigorously examine changes in crime by county in Pennsylvania, West Virginia, and Ohio, paying special attention to trends in counties by the number of wells drilled. Because levels of crime vary with the size of the local population, we analyzed crime per 100,000 individuals to facilitate comparisons of the crime rate by county. Our analysis in this chapter focused on reported offenses for violent and property crime. Violent crime is defined as reported offenses for murder, negligent manslaughter, rape, robbery, and aggravated assault. Property crime is defined as reported offenses for burglary, larceny, motor vehicle theft, and arson. We relied on data on criminal offenses through 2012 published by the Pennsylvania State Police (starting in 1999), the West Virginia State Police (starting in 2002), and the Ohio Department of Public Safety (starting in 2000). Reflecting the data available, we also present crime rates for lesser criminal offenses for Pennsylvania and West Virginia.

Pennsylvania:

Figure 4.1



Note. Violent crime is defined here as reported offenses for murder, negligent manslaughter, rape, robbery, and aggravated assault.
Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

As illustrated in Figure 4.1 (see also the Online Technical Appendix, Chapter 4, Table D6), violent crime rates were rising between 2001 and 2005 in counties that would eventually see the biggest expansion of drilling, a pattern similar to the rest of the state. However, since 2005 the violent crime rate in the heaviest drilling counties has climbed by 16%, while crime rates have for the most part held steady or fallen in the rest of the state's counties (including those with fewer wells and those in urban and rural communities without wells). This rise in violent crime in the heaviest drilling counties resulted mainly from an increase in aggravated assaults.[18]

Table 4.1 presents the violent crime rate in Pennsylvania counties with 100 or more wells drilled as well as the crime rate in rural and urban counties with no wells drilled (See Map 1.1 in Chapter 1). Since 2005, violent crime was up in every county with more than 400 wells. The violent crime rate fell in all but two (Westmoreland and Clearfield) of the counties with between 100 and 399 wells. The violent crime rate was down in both urban and rural communities without wells drilled. Besides aggravated assault, the other quantitatively important major violent crime category is robbery-theft; this has not shown a

[18] Aggravated assault is one of the two largest components of violent crime, accounting for more than half of the violent criminal offenses (see the Online Technical Appendix, Chapter 4, Table D7). Between 2005 and 2012, aggravated assault has risen by 13% in counties with 400 or more wells (see the Online Technical Appendix, Chapter 4, and Table D12).

significant increase in any of the drilling areas since the emergence of major fracking activity in 2005. (The remaining violent crime categories—murder, negligent manslaughter, and rape—do not represent a large share of violent crime and have seen minimal to zero growth.)

Table 4.1

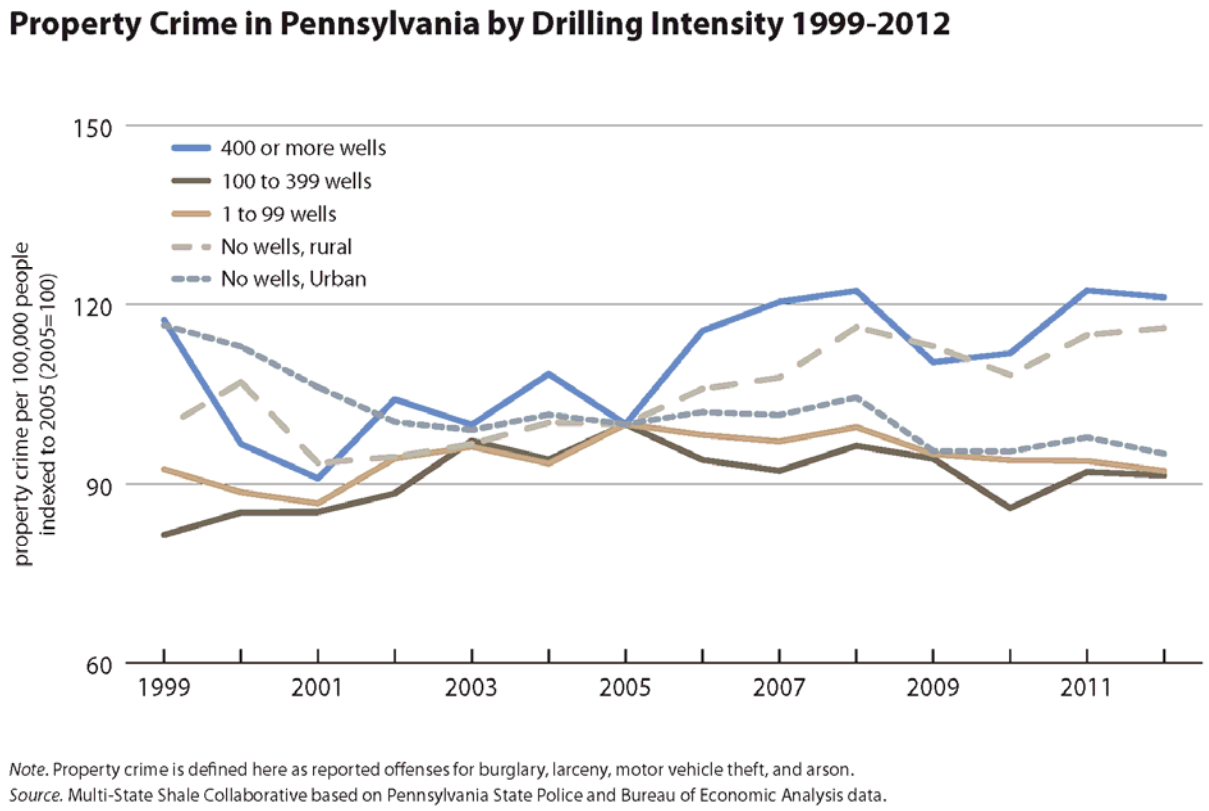
Violent crime in Pennsylvania counties with 100 or more wells drilled and in urban and rural counties with no wells

Wells drilled/region	Violent crime per 100,000 people in 2012	1999 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
Urban, no wells	444	-10	-2%	-87	-16%	0
Rural, no wells	208	20	10%	-14	-6%	0
Bradford	145	-57	-33%	31	28%	1126
Tioga	113	-12	-19%	62	123%	811
Washington	184	4	2%	10	6%	755
Lycoming	181	7	4%	7	4%	662
Susquehanna	126	-48	-31%	18	16%	646
Greene	184	-74	-45%	93	103%	517
Westmoreland	154	-26	-15%	1	1%	230
Fayette	254	110	58%	-45	-15%	230
Butler	114	50	35%	-83	-42%	174
Clearfield	304	-18	-8%	94	45%	147
Armstrong	96	43	50%	-34	-26%	146
Wyoming	100	50	59%	-35	-26%	112

Note. Violent crimes are reported offenses for murder, negligent manslaughter, rape, robbery, and aggravated assault.

Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

Property Crime in Pennsylvania:
Figure 4.2



Note. Property crime is defined here as reported offenses for burglary, larceny, motor vehicle theft, and arson.
Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

The property crime rate also rose between 2001 and 2005 in counties with 400 or more wells drilled. Since 2005, property crime increased another 21% in counties with 400 or more wells (Figure 4.2 and Online Technical Appendix, Chapter 4, Table D8). Over the same period the rate of property crime was down in urban counties with no wells as well as counties with fewer than 400 wells.[19] Rural Pennsylvania counties without wells, however, saw the rate of property crime climb over the period by 16%, not far below the increase for high-drilling counties. As with violent crime, all six counties that had 400 or more wells experienced an increase in property crime. The most abrupt increases were seen in the two heaviest-drilling counties, Bradford and Tioga, with 83% and 54% increases, respectively, and in Greene County, which experienced the biggest total employment increase (Table 4.2).

Larceny thefts represent the bulk of property crime (69% to 73% of property crimes between 1999 and 2012), and the rate of larceny theft in Pennsylvania has increased 25% in counties with 400 or more wells (see the Online Technical Appendix, Chapter 4, Table D9 and Table D10). The rate of larceny theft was

[19] The estimated number of property crimes decreased by 9% in counties with 100-399 wells, 8% in counties with 1-99 wells, and 5% in urban counties with no drilling activity.

also up 21% in rural counties with no drilling activity. The rate of larceny theft fell in drilling counties with fewer than 400 wells as well as in urban counties with no wells.[20]

Table 4.2

Property crime in Pennsylvania counties with 100 or more wells drilled and in urban and rural counties with no wells

Wells drilled/region	Property crime per 100,000 people in 2012	1999 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		change	percent change	change	percent change	
Urban, no wells	2425	-421	-14%	-126	-5%	0
Rural, no wells	1766	10	1%	244	16%	0
Bradford	1965	-630	-37%	890	83%	1126
Tioga	1444	-266	-22%	509	54%	811
Washington	1707	-147	-9%	144	9%	755
Lycoming	2170	-349	-15%	201	10%	662
Susquehanna	1204	-234	-17%	86	8%	646
Greene	2001	39	3%	694	53%	517
Westmoreland	1472	219	16%	-133	-8%	230
Fayette	2488	931	61%	34	1%	230
Butler	1281	112	7%	-409	-24%	174
Clearfield	2268	455	25%	15	1%	147
Armstrong	931	169	18%	-158	-15%	146
Wyoming	1419	55	4%	48	3%	112

Note: Property crimes are reported offenses for burglary, larceny, motor vehicle theft, and arson.

Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

[20] Burglary, another subcategory making up 19% of property crime on average, has also shown an increase in heavily drilled counties. In areas with the most drilling activity, there has been a 30% increase in burglary from 2005 to 2012, compared to a 13% decline between 1999 and 2005. Motor vehicle theft, which composes about 9% of property crime in Pennsylvania, has continued to plummet in counties with drilling. Arson has seen virtually no change since 1999.

Other Categories of Crime in Pennsylvania:

Table 4.3

Drug abuse in Pennsylvania by the number of wells drilled

Wells drilled/region	Drug abuse per 100,000 people in 2012	1999 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
400 or more wells	360	52	27%	116	48%	4517
100 to 399 wells	247	148	92%	-63	-20%	1039
1 to 99 wells	403	98	39%	51	14%	695
Rural, no wells	281	56	33%	56	25%	0
Urban, no wells	463	60	15%	3	1%	0

Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

In addition to violent and property crime, the Pennsylvania State Police also track 18 other categories of less serious criminal offenses.[21] Of these 18 crimes, just six (vandalism, other assaults, DUI, disorderly conduct, drug abuse, and all other offenses) represent more than 80% of these less serious criminal offenses. Among these offenses, the changes in the crime rate for drug abuse and DUIs stand out in counties with 400 or more wells.[22] Prior to the start of drilling, the period from 1999 to 2005, the rate of reported criminal offenses for drug abuse rose 27% in counties that would see the biggest increase in drilling (Table 4.3 and Figure 4.3). Between 2005 and 2012 the crime rate for drug abuse rose 48% in the heaviest drilling counties, it rose 25% in rural areas without wells and just 1% in urban areas without wells . DUI offenses were up 65% since 2005 in the heaviest drilling counties in Pennsylvania. DUI offenses were up 42% over the same period in the rural counties without wells and up just 5% in urban counties without wells.

Table 4.4

DUI offenses in Pennsylvania by the number of wells drilled

Wells drilled/region	DUI cases per 100,000 people in 2012	1999 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
400 or more wells	543	-60	-15%	214	65%	4517
100 to 399 wells	408	49	14%	2	0%	1039
1 to 99 wells	398	37	11%	22	6%	695
No wells, rural	445	-17	-5%	133	42%	0
No wells, urban	400	73	24%	21	5%	0

Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

[21] These include reported offenses for other assaults, forgery, fraud, embezzlement, stolen property, vandalism, weapons (carrying, possession, etc.), prostitution, sex offenses, drug abuse, gambling, family offense, DUIs, liquor law violations, drunkenness, disorderly conduct, vagrancy, and all other offenses.

[22] In the remaining categories in the heaviest drilling areas, there was little change in the number of reported offenses over the period studied.

Box 4.1: Drug Abuse and Drilling

As drilling has expanded in West Virginia and Pennsylvania, local concerns that the employment boom benefited out-of-state workers have, at times, been rebuffed with claims that the local workforce was plagued by rampant drug abuse, which severely limited the pool of labor available to drillers. For example, in the city of Williamsport (Lycoming County) a recent article on the region's struggle with drug abuse led a local chamber of commerce official to note:

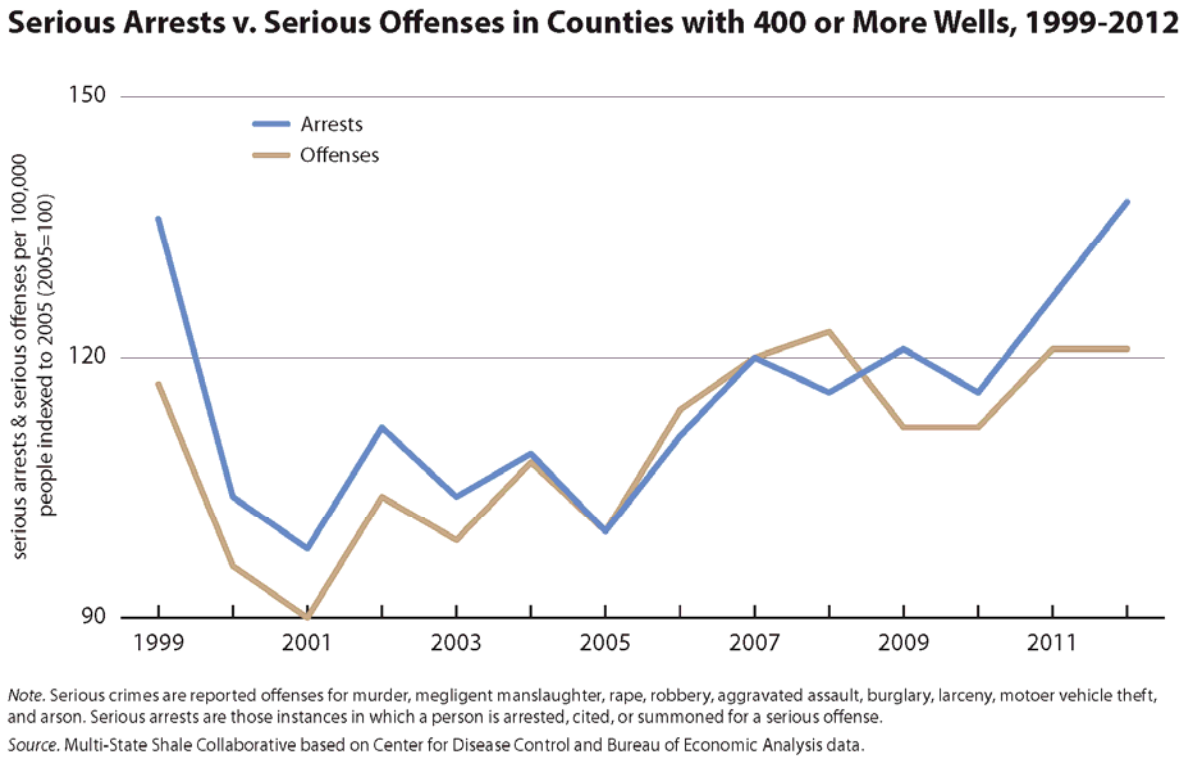
> The unemployment rate has gone down thank to jobs being created by companies involved with the natural gas exploration and drilling along the Marcellus Shale. But employers are having trouble filling certain positions because applicants can't pass a drug test, said Vincent J. Matteo, president and chief executive officer of the Williamsport-Lycoming Chamber of Commerce.[1]

These claims have never been substantiated by data on the number of workers that have failed drug tests when applying for employment with drillers. In general, the rate at which workers in Pennsylvania fail employment-related drug tests, including in drilling regions, is less than 5% (see Page 21) and, therefore, is unlikely to be an important determinant of the mix of local and out-of-state residents employed directly or indirectly in the development of shale oil and gas. As the data on drug abuse summarized in Table 4.4 make clear, the expansion of drilling and drug abuse are not phenomena independent of one another. For policymakers and communities contemplating the expansion of shale oil and gas extraction, these data point to the need for community-wide plans to address the challenges that come with increased drug abuse.

[1] A. John Beauge, "'Home of millionaires' has new meaning in Williamsport - heroin sales," *Patriot News*, June 14, 2014. http://goo.gl/vWcIIh]

Arrest Data for Pennsylvania:

Figure 4.3



Note. Serious crimes are reported offenses for murder, megligent manslaughter, rape, robbery, aggravated assault, burglary, larceny, motoer vehicle theft, and arson. Serious arrests are those instances in which a person is arrested, cited, or summoned for a serious offense.

Source. Multi-State Shale Collaborative based on Center for Disease Control and Bureau of Economic Analysis data.

The Pennsylvania State Police, in addition to tracking data on reported offenses, also track data on arrests. The arrest data corroborate our earlier analysis of violent and property crime data. In heavily drilled areas the increase in the overall rate of crime since 2005 (the sum of all violent and property crimes) has also been accompanied by a rise in the rate of arrests (Figure 5.3).

Considering arrests for all violent and property crime categories, the increase in arrests has been primarily for aggravated assault and larceny theft (see Online Technical Appendix, Chapter 4, Table D11).

West Virginia

Our analysis of West Virginia crime data reveals no clear relationship between increased drilling and crime rates. From 2005 to 2012, there was a 49% increase in violent crime rates in West Virginia rural counties with no wells. The changes in crime rates in West Virginia counties with 100 more wells over this period was above 49% in three counties and below 49% in seven counties. We also found no relationship between drilling and property and "all other" crime (see the Online Technical Appendix, Chapter 4 Table D1, Table D2 and Table D3 for crime rates in West Virginia).

Ohio

Although we do observe an increase in both property and violent crime since the start of drilling in Carroll County, the heaviest drilling county in Ohio, both crime rates prior to the start of drilling rose and fell by similar amounts, making it difficult to confidently conclude that the modest amount of drilling is the primary driver of the changes in the crime rate that have occurred since 2009.

The violent and property crime rates were up in rural areas with no drilling by 8% and 5%, respectively, since 2009 (See the Online Technical Appendix, Chapter 4, Table D4 and Table D5). In urban counties with no drilling the violent and property crime rates were down by 11% and 6%, respectively.

Panel regression on violent and property crime

Using our data set (2000 to 2012) of violent and property crime rates (expressed in logs), we estimated using a fixed effects panel regression the relationship between crime rates and the amount of drilling activity by county in West Virginia, Pennsylvania and Ohio. We included three indicator variables set to 1 for counties between 2005 and 2012 (the period in which drilling occurred) that also had high-activity (400 or more wells drilled over the period), medium-activity (100 to 399 wells drilled over the period) and low-activity (1 to 99 wells drilled over the period) and zero otherwise.[23] For both violent and property crime in high-activity counties after 2005, we found positive and statistically significant elasticities indicating violent crime was up 17.7%,and property crime was up 10.8%.. The coefficient for medium-activity counties was not statistically significant. For low-activity counties there was positive and statistically significant elasticity for violent crime but not for property crime.

[23] As reflected in the absence of a full set of controls, our intent here is not to fully explain differences in crime rates across counties but to make a first attempt at assessing the relationship between drilling and crime rates. Researchers interested in exploring the robustness of this relationship can find this dataset in the Online Technical Appendix, Chapter 4, AppendixD.dta (stata).

Table 4.5

Violent and property crime rates in drilling counties in West Virginia, Pennsylvania and Ohio by high-, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of the number of violent crimes per 100,000 people	Dependent variable = natural log of the number of property crimes per 100,000 people
	b/se	b/se
High-activity	0.177***	0.108***
	(0.059)	(0.038)
Medium-activity	-0.040	-0.009
	(0.071)	(0.061)
Low-activity	0.165***	0.022
	(0.044)	(0.047)
Constant	4.801***	7.351***
	(0.011)	(0.012)
R-sqr-overall	0.002	0.006
N	2,639	2,660

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels. Standard error estimates are robust to disturbances being heteroscedastic.

Chapter 5: Sexually Transmitted Diseases

Sexually transmitted diseases have increased in some areas where transient workers, mostly young men, enter a new town en masse to work in the gas (or related) industries. Food and Water Watch found that in Pennsylvania the average number of cases of sexually transmitted diseases was 62 percent higher in heavily drilled counties than in counties with no drilling (Food and Water Watch 2013). The Troy Community Hospital in Bradford County, Pennsylvania (home to the highest number of wells in the three-state region), reported an increase in STDs connected to the growth of the industry (Covey 2011). A spike in sexually transmitted diseases has also been reported in highly drilled areas in other states, including Carrizzo Springs, Texas; Mesa County, Colorado; and McKenzie County, North Dakota (Vaughan 2012; Redifer et al 2007; Eligon 2013). Chlamydia rates doubled between 2010 and 2011 in McKenzie County, North Dakota (Eligon 2013).

Case Study Findings

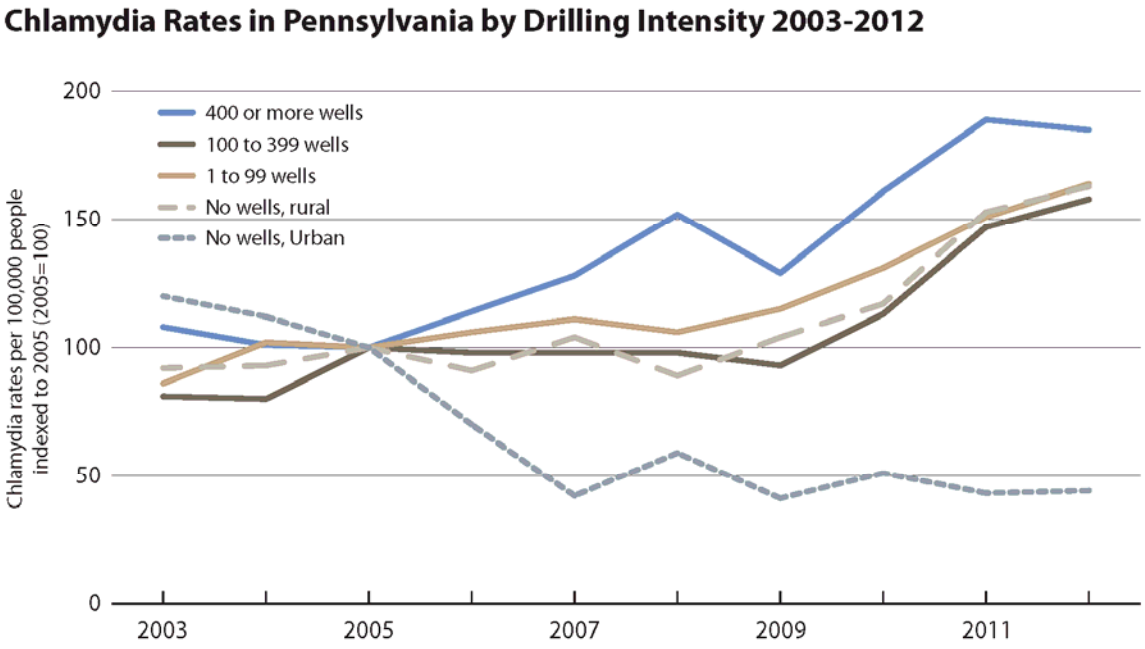
In our case studies of high-drilling counties, only Tioga County respondents reported increases in sexually transmitted diseases. In Tioga County, Pennsylvania's Soldiers and Sailors Memorial Hospital said an increase in sexually transmitted diseases was one clear impact it has seen as a result of increased drilling. Executive Vice President Ron Butler reported that the hospital traced this increase to individuals who had out-of-state home addresses, likely connected to the gas drilling industry (Ward, Polson, and Price 2014). County-level data show that chlamydia rates in Tioga County rose 93% between 2005 and 2012 (compared to rural, non-drilling counties, which saw rates rise 63%). Gonorrhea rates rose only slightly higher (46%) than statewide rates (which rose 37%).

While local Greene County, Pennsylvania, and Wetzel County, Ohio, informants did not report increased rates of STDs, county data showed that rates for chlamydia did rise 119% between 2005 and 2012 in Greene County (nearly double the rate of growth in rural non-drilling Pennsylvania counties) and 146% in Wetzel County (compared to 81% in non-drilling rural West Virginia counties). Carroll County, Ohio, has so far seen a much lower chlamydia rate increase (3%) than rural non-drilling Ohio counties (where rates rose 55%). Gonorrhea rates also rose in some of our case study counties (46% in Tioga County and 266% in Greene County, compared to 37% in rural non-drilling PA counties).[24] Wetzel County, WV, had an increase of 56% in gonorrhea rates, compared to rural, non-drilling WVA counties, where the rates rose only 11%.

[24] The exception was Carroll County, Ohio, which saw rates decrease between 2005 and 2012.

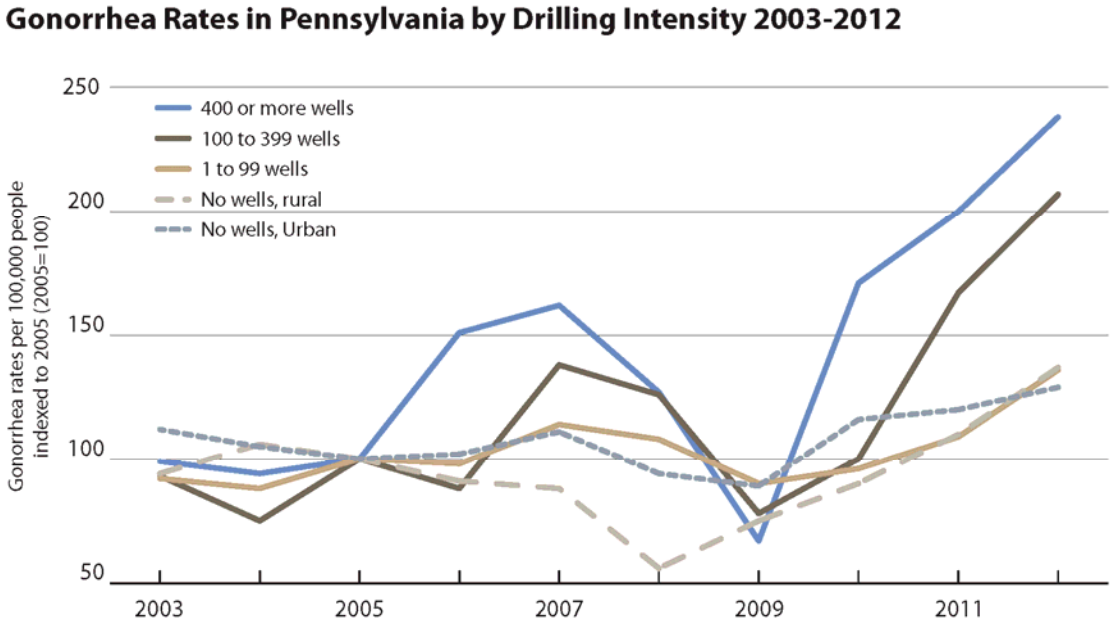
Sexually transmitted disease by county:

Figure 5.1



Source. Multi-State Shale Collaborative based on Center for Disease Control and Bureau of Economic Analysis data.

Figure 5.2



Source. Multi-State Shale Collaborative based on Center for Disease Control and Bureau of Economic Analysis data.

We looked at all six Pennsylvania high- activity drilling counties and how their STD rates compared with counties that have less drilling as well as rural and urban counties with no drilling.

For chlamydia rates (see Figure 5.1 and the Online Technical Appendix, Chapter 5, Table E1. See Table E3 for infection rates for individual Pennsylvania counties with 100 or more wells).All rural areas (with and without drilling) experienced big incidence rate increases while urban areas experienced a big reduction in incidence. High-activity drilling counties, however, experienced the biggest increase in rates (85% compared with 58% to 63% in the three other rural groupings).

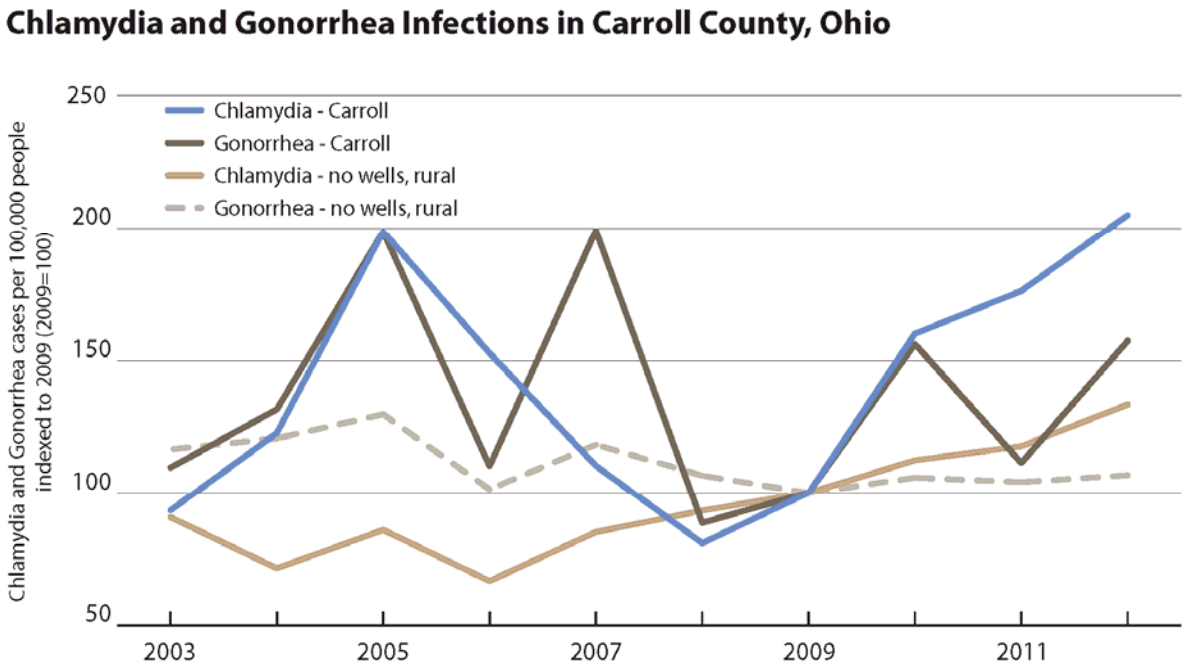
For gonorrhea rates see Figure 5.2 and see the Online Technical Appendix, Chapter 5, Table E2. See Table E4 for infection rates for individual Pennsylvania counties with 100 or more wells. The gonorrhea picture was more mixed with rates of infection rising in every part of Pennsylvania (especially since 2009). The heaviest drilling counties experienced the largest increase in rate of infection from 2005 to 2012 (138%), followed by counties with 100 to 399 wells (107%). Counties with less or no drilling only experienced incidence rate increases of about 30% to 40%.

Possibly as a result of the lower level of drilling, there was no clear relationship between rates of infection for either chlamydia or gonorrhea in West Virginia and the amount of drilling (See Table E5 and Table E6 in Chapter 5 of the Online Technical Appendix).

Tables 5.1 and 5.2 show that Carroll County, Ohio, experienced, relative to the rest of the state, a larger increase in the incidence of chlamydia.[25] Gonorrhea was also up across drilling counties in Ohio. Given the low level of drilling and the volatility of data on infectious disease for a small rural county like Carroll, this data is only suggestive of a link between drilling and the spread of sexually transmitted disease in Ohio.

[25] Because drilling began later in Ohio, we analyzed changes in the number of cases of chlamydia and gonorrhea per 100,000 people before and after 2009.

Figure 5.3



Source. Multi-State Shale Collaborative based on Center for Disease Control and Bureau of Economic Analysis data.

Table 5.1

Chlamydia rates in Ohio by the number of wells drilled

Wells drilled/region	Chlamydia cases per 100,000 people in 2012	2003 to 2009		2009 to 2012		Total wells drilled 2009 to 2012
		Change	Percent change	Change	Percent change	
Carroll county	262	9	7%	134	105%	112
1 to 99 wells	206	6	4%	57	38%	158
No wells, rural	265	19	10%	66	33%	0
No wells, urban	57	26	54%	-18	-23%	0

Source. Multi-State Shale Collaborative based on Centers for Disease Control and Prevention and Bureau of Economic Analysis data.

Table 5.2

Gonorrhea rates in Ohio by the number of wells drilled

Wells drilled/region	Gonorrhea cases per 100,000 people in 2012	2003 to 2009		2009 to 2012		Total wells drilled 2009 to 2012
		change	percent change	change	percent change	
Carroll County	49	-3	-9%	18	57%	112
1 to 99 wells	81	-50	-49%	30	58%	158
No wells, rural	42	-6	-14%	3	7%	0
No wells, urban	195	-65	-26%	12	7%	0

Source. Multi-State Shale Collaborative based on Centers for Disease Control and Prevention and Bureau of Economic Analysis data.

Panel regression on sexually transmitted disease

Using our data set (2003 to 2012) of chlamydia and gonorrhea rates (expressed in logs), we estimated using a fixed effects panel regression the relationship between each of these sexually transmitted diseases and the amount of drilling activity by county in West Virginia, Pennsylvania and Ohio. We used three indicator variables set equal to 1 for counties between 2005 and 2012 (the period in which drilling occurred) that also had high-activity (400 or more wells drilled over the period), medium-activity (100 to 399 wells drilled over the period) and low-activity (1 to 99 wells drilled over the period) and 0 otherwise.[26] Matching the patterns we observed in the descriptive data summarized earlier in this chapter, we found evidence of a link between drilling and the incidence of chlamydia but not for the incidence of gonorrhea. Specifically, we found a positive and statistically significant elasticity for chlamydia in drilling counties after 2005 for all levels of drilling activity, indicating between a 24% and 27% increase in the incidence of chlamydia. With respect to gonorrhea, the coefficients for high- and

[26] The results here do not represent a full accounting of the factors that explain differences between counties in the incidence of sexually transmitted diseases. These results provide a first test of the association between drilling and the incidence of sexually transmitted disease. Researchers interested in further exploring the strength of this relationship can find this dataset in the Online Technical Appendix, Chapter 5, AppendixE.dta (stata).

medium-activity counties are not statistically significant. We did find for gonorrhea in low- activity counties a negative (lower incidence of infection) and statistically significant effect.

Table 5.3

Chlamydia and gonorrhea rates in drilling counties in West Virginia, Pennsylvania and Ohio by high, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of the number of chlamydia cases per 100,000 people	Dependent variable = natural log of the number of gonorrhea cases per 100,000 people
	b/se	b/se
High-activity	0.260***	-0.171
	(0.051)	(0.217)
Medium-activity	0.243***	-0.099
	(0.058)	(0.131)
Low-activity	0.274***	-0.125**
	(0.046)	(0.063)
Constant	4.780***	3.281***
	(0.015)	(0.020)
R-sqr-overall	0.002	0.046
N	1,929	1,896

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels. Standard error estimates are robust to disturbances being heteroscedastic.

Chapter 6: Motor Vehicle Fatalities

In a study of two Barnett Shale counties, Anderson and Theodori (2009) report that "Some communities have tied increased traffic accidents and fatalities to the traffic from shale development."

In Bradford County, Pennsylvania, Stacy Covey, president of Guthrie Troy Community Hospital, found that traffic accidents, along with increases in STDs, occupational injuries, and substance abuse, put pressure on local hospitals (Covey 2011).

In Pennsylvania, local officials cited traffic, safety, and road damage as key concerns (Schaeffer 2011;Troxell 2011) (Herzenberg, Polson and Price 2014).

Case Study Findings

The Multi-State Shale Collaborative case studies in West Virginia, Pennsylvania and Ohio found an increase in heavy truck traffic due to increased industry activity. Deteriorated roads, increased noise, safety concerns, and higher road repair costs became major concerns in these areas as drilling advanced.

Interviews revealed a widely shared concern about truck drivers operating their vehicles unsafely. Truck driver safety is particularly important given the increase in trucks on the road in these rural counties. One Pennsylvania Department of Transportation (PennDOT) official in Tioga County said that traffic volume had increased from 50 or 60 vehicles per day to 400 trucks on the same roads to accommodate the volume of gas drilling in the county (Ward, Polson, and Price 2014).

School officials in Tioga County reported concerns about children's safety. School bus drivers experienced "a number of close calls and near misses," said one school official. "Some gas trucks were going pretty fast around the buses" (Ward, Polson, Price 2014, p. 13). Greene County officials reported that truck drivers do not always adhere to speed limits and stop signs, endangering pedestrians and other drivers (Herzenberg, Polson, and Price 2014). In Wetzel County, WV, county commissioners cited road safety as their biggest concern, adding that many of the subcontractors and trucking companies violate traffic laws, including speeding and driving left-of-center (O'Leary 2014).

The case studies also provided anecdotal data on traffic fatalities. In Greene County, PA, traffic fatalities ranged from 5 to 16 per year between 2000 and 2012, but the highest number of fatalities occurred in 2012, the peak of gas drilling locally (Herzenberg, Polson, Price 2014, p 17). In Carroll County, OH, one transportation expert reported that "Before shale development, there might have been one or two accidents a year involving semi-trucks, and five years might pass without a rollover incident. Over the last year, however, there have been several large vehicle rollovers in the county; a trucker and a community member recently died." (Woodrum 2014)

Some interviewees reported the need for more emergency services personnel because of increased traffic and accidents. In Carroll County, OH, reported traffic incidents doubled, and calls to the sheriff quadrupled since the start of drilling there. To deal with the increased calls, EMS had to add extra shifts, and the county needed an assistant director of emergency management and additional deputies (Woodrum 2014). Helicopter transport has increased 200% in Tioga County, PA, due to changing protocols for medical transport, population growth, and the increased number of vehicle accidents (Ward, Polson, Price 2014).

Motor vehicle fatalities by county

We analyzed data on traffic fatalities compiled annually by the National Highway Traffic Safety Administration. In order to compare data across counties with differing populations, we expressed the number of fatalities in each county and group of counties as the number of fatalities per 100,000 people (Table 6.1).

All across Pennsylvania traffic fatalities were on the rise from 2000 to 2005. Since 2005, traffic fatalities have fallen in both urban and rural counties without wells. Counter to this trend, traffic fatalities continued to rise in the six Pennsylvania counties with 400 or more wells (see the Online Technical Appendix, Chapter 6, Table F1, for a county-by-county breakout of rates of traffic fatalities in Pennsylvania counties with 100 or more wells). Translating the continued upward trend in traffic fatality rates into actual deaths, given that these counties collectively have a population of slightly more than half a million people, Pennsylvania's six high-drilling counties experienced about 35 more traffic fatalities in 2012 than if the number of fatal accidents per 100,000 had followed the statewide trend.

In West Virginia and Ohio, the county-level data reveal no systematic relationship between drilling and traffic fatalities. (See the Online Technical Appendix, Chapter 6, Table F2, for county-by-county data).

Truck-involved motor vehicle fatalities by county

We analyzed data provided by the Center for the Management of Information for Safe and Sustainable Transportation (http://www.cmisst.org/tifa/) on trucks involved in fatal accidents. As these data are only available through 2010, we do not report trends for Ohio because there were only four wells drilled in the state in that year.

With the exception of urban counties without wells, traffic fatalities involving trucks were up from 2000 to 2005 in Pennsylvania (Table 6.2). After 2005, fatalities involving trucks were down in both urban and rural counties without wells. Truck-involved fatalities, however, rose in the six Pennsylvania counties with 400 or more wells as well as in Pennsylvania counties with 100 or more wells (see the Online Technical Appendix, Chapter 6, Table F3, for a county-by-county breakout of rates of traffic fatalities in Pennsylvania counties with 100 or more wells). In the six high-drilling counties, there were 10 more fatalities involving trucks in 2012 than if these counties had followed the statewide average.

In West Virginia, fatalities involving trucks were down since the start of drilling in both the heaviest drilling counties and in rural and urban counties without wells (see the Online Technical Appendix, Chapter 6, Table F4, for a county-by-county breakout of rates of traffic fatalities in West Virginia counties with 100 or more wells drilled). Truck-involved traffic fatalities were up slightly in West Virginia counties with fewer than 100 wells.

Table 6.1

Fatal accidents per 100,000 people by state and number of wells drilled

Wells drilled/region	Fatal accidents per 100,000 people in 2012	2000 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
PA, 400 or more wells	19.5	2.9	21%	2.5	14%	4517
PA, 100 to 399 wells	16.2	0.6	4%	-0.3	-2%	1039
PA, 1 to 99 wells	10.7	0.5	4%	-3.4	-24%	695
PA, Rural	15.7	2.8	15%	-6.7	-30%	0
PA, Urban	7.8	0.2	2%	-2.4	-23%	0
WV, 100 to 399 wells	17.6	-6.7	-25%	-2.5	-12%	1432
WV, 1 to 99 wells	19.2	-1.1	-5%	-2.4	-11%	700
WV, Rural*	28.5	5.7	26%	0.6	2%	0
WV, Urban*	15.0	-1.1	-6%	-2.2	-13%	0
OH, 100 to 399 wells	10.5	-0.1	-1%	-3.2	-24%	112
OH, 1 to 99 wells	10.6	-2.0	-14%	-1.8	-15%	158
OH, Rural*	14.5	-1.2	-6%	-3.6	-20%	0
OH, Urban*	7.5	0.1	1%	-1.0	-12%	0
MD, Rural*	12.8	-0.6	-4%	-3.0	-19%	0
MD, Urban*	6.9	0.0	0%	-2.1	-24%	0
NY, Rural~	1.3	-0.3	-15%	-0.1	-6%	22
NY, Urban*	0.4	0.0	-7%	-0.2	-26%	0
VA, Rural~	20.1	3.6	15%	-7.6	-27%	93
VA, Urban*	14.9	-2.9	-13%	-3.8	-21%	0

*The figures here represent fatal accidents in rural and urban counties with no wells drilled between 2002 and 2012.

~There were 93 wells drilled in rural Virginia counties, and 22 wells drilled in rural New York counties between 2002 and 2012.

Note. A county or county group is defined as rural if the 2005 population per square mile in that county is below its corresponding statewide total population per square mile. What follows is the population per square mile for each state in this study: Pennsylvania (278); West Virginia (75); Maryland (576); New York (405); Ohio (280); Virginia (191).

Source. Multi-State Shale Collaborative based on National Highway Traffic Safety Administration and Bureau of Economic Analysis data.

Table 6.2

Fatal accidents per 100,000 people involving trucks by state and number of wells drilled

Wells drilled/region	Fatal accident rate per 100,000 people involving trucks in 2010	2000 to 2005		2005 to 2010		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
PA, 400 or more wells	3.7	0.8	44%	1.2	46%	4517
PA, 100 to 399 wells	3.5	0.4	20%	1.3	59%	1039
PA, 1 to 99 wells	1.2	0.1	7%	-0.5	-29%	695
PA, Rural	2.3	0.9	48%	-0.5	-17%	0
PA, Urban	0.8	-0.1	-9%	-0.4	-35%	0
WV, 100 to 399 wells	2.1	-0.9	-24%	-0.7	-25%	1432
WV, 1 to 99 wells	3.2	0.0	0%	0.3	10%	700
WV, Rural*	1.3	5.3	379%	-5.4	-81%	0
WV, Urban*	1.0	-0.3	-18%	-0.6	-37%	0
OH, Rural*	1.7	-0.9	-25%	-0.9	-33%	0
OH, Urban*	0.7	0.1	6%	-0.3	-28%	0
MD, Rural*	1.2	-0.2	-8%	-0.9	-41%	0
MD, Urban*	0.3	-0.1	-7%	-0.5	-58%	0
NY, Rural~	1.3	-0.3	-15%	-0.1	-6%	22
NY, Urban*	0.4	0.0	-7%	-0.2	-26%	0
VA, Rural~	2.8	0.7	24%	-1.1	-28%	93
VA, Urban*	1.7	0.1	3%	-0.7	-29%	0

*The figures here represent trucks in fatal accidents in rural and urban counties with no wells drilled between 2002 and 2012.

~There were 93 wells drilled in rural Virginia counties, and 22 wells drilled in rural New York counties between 2002 and 2012.

Note. A county or county group is defined as rural if the 2005 population per square mile in that county is below its corresponding statewide total population per square mile. What follows is the population per square mile for each state in this study: Pennsylvania (278); West Virginia (75); Maryland (576); New York (405); Ohio (280); Virginia (191).

Source. Multi-State Shale Collaborative based on Center for the Management of Information for Safe and Sustainable Transportation and Bureau of Economic Analysis data.

Panel regression on motor vehicle fatalities

Our data set of fatal motor vehicle accidents by county covered the period from 2000 to 2012, while our data set of fatal motor vehicle accidents involving trucks covered the period from 2000 to 2010. We examined changes in the rate of these fatalities (expressed in logs) using a fixed effects panel regression for counties in West Virginia, Pennsylvania and Ohio. We used three indicator variables set equal to 1 for counties between 2005 and the end of the period (the period in which drilling occurred) that also had high- activity (400 or more wells drilled over the period), medium-activity (100 to 399 wells drilled over

the period), and low-activity (1 to 99 wells drilled over the period), and 0 otherwise.[27] In high-activity counties, only the coefficient for truck-involved motor vehicle fatalities was statistically significant and positive, indicating a 27.8% increase in truck-involved fatalities. Both coefficients (all fatal motor vehicle accidents and truck-involved fatal motor vehicle accidents) for medium-activity counties were not statistically significant. For low-activity counties, only the coefficient for all motor vehicle fatalities was significant, and it was negative.

Table 6.3

Fatal motor vehicle accidents overall and those involving trucks in West Virginia, Pennsylvania and Ohio drilling counties by high-, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of the number of motor vehicle accidents per 100,000 people (2000 to 2012)	Dependent variable = natural log of the number of fatal motor vehicle accidents involving trucks per 100,000 people (2000 to 2010)
	b/se	b/se
High-activity	0.017	0.278**
	(0.081)	(0.133)
Medium-activity	-0.030	-0.095
	(0.052)	(0.117)
Low-activity	-0.111***	-0.048
	(0.032)	(0.050)
Constant	2.809***	0.968***
	(0.008)	(0.010)
R-sqr-overall	0.004	0.000
N	2,672	1,569

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels. Standard error estimates are robust to disturbances being heteroscedastic.

[27] The results here do not represent a full accounting of the factors that explain differences between counties in fatal motor vehicle fatalities. These results provide a limited test of the association between drilling and fatal motor vehicle accidents. Researchers interested in further exploring the strength of this relationship can find this dataset in the Online Technical Appendix, Chapter 6, AppendixF.dta (stata).

Chapter 7: Rental Housing Markets

Ecosystems Research Group (2009) documented large population increases associated with natural resource extraction in Sublette County, Wyoming, between 2000 and 2006which, in turn, boosted housing prices and rents there relative to Wyoming as a whole. In case studies of energy development in Mesa and Garfield counties, Colorado, and Sweetwater County, Wyoming, Headwaters Economics (2008; 2009) reported a shortage of housing resulting from energy-related development. In both their reports, Headwaters found that non-energy-related employers, including local colleges and hospitals, had difficulty recruiting new workers because of the sharp rise in the cost of housing. Headwaters noted that the high wages of oil and gas companies, relative to what other employers in the region were paying, put upward pressure on rents and housing prices and potentially threatened the economic diversity of regional economies. Ecosystems Research Group raised similar concerns when comparing housing affordability and pay for energy-related and non-energy-related employment in Sublette County, Wyoming. Jacquet (2009), in summarizing literature focused on an energy boom in the western United States in the 1970s, cited similar themes of housing shortages and rising home prices and rents. Jacquet also noted evidence of an expansion of mobile home communities and an increased commute as among the responses to the housing shortages experienced in the 1970s.

Recent research has identified other potential impacts. Property values near drilling activity, particularly homes with well water, can be negatively impacted (Gopalakrishnan and Klaiber 2012; Muehlenbacks, Sipplier, and Timmins 2012; BBC Research and Consulting; Integra Realty Resources; Colorado School of Public Health 2011).

Case Study Findings

Our case studies of four drilling counties revealed findings consistent with other research on housing impacts of booms in extractive industries. Out-of-state drilling industry workers created increased demand for temporary housing in Carroll, Greene, and Tioga counties (Woodrum 2014; Herzenberg, Polson, and Price, 2014; Ward, Polson, and Price, 2014). Hotels filled up and new hotels were added or planned. For example, the hotel in Carrollton, Ohio, had been solidly booked for two years, and there were plans to build a new one (Woodrum 2014). The most pronounced housing impact in Wetzel County was a 700% increase in collections from a New Martinsville hotel room occupancy tax, primarily in 2011 and 2012 (O'Leary 2014). Tioga and Greene counties each built two new hotels. Their hotel occupancy tax does not apply to stays over 30 days, so the counties lost significant revenue to long stays. (Coolidge 2011; Herzenberg, Polson, and Price 2014). An informant in Tioga County said the hotel shortage hurt the county's tourism business, and an informant in Greene County said tourists often spend their lodging dollars outside the county because of a lack of available rooms (Coolidge 2011; Herzenberg, Polson, and Price 2014).

In Tioga, Greene, and Carroll counties, empty lots were being turned into RV sites, sometimes without adequate connections to water, sewer, or electrical systems (Woodrum 2014, Herzenberg, Polson, and Price, 2014; Ward, Polson, and Price, 2014). According to a local joke in Greene County, "$900 will get you a pond-side view."

Large housing stipends for oil and gas workers and limited supplies of housing translated into a doubling, tripling, or even quadrupling of rental rates since the start of drilling Carroll County, Ohio, according to local interviews (Woodrum 2014). In Tioga County, classified ads in the *Wellsboro Gazette* documented a

doubling or tripling of rents for comparable housing between 2007-08 and 2012 (Ward, Polson, and Price, 2014).

Rising rents, in turn, created a shortage of affordable housing in Carroll County (Boyd 2013). In Greene County, increased demand exacerbated a pre-existing shortage of affordable housing (Herzenberg, Polson, and Price, 2014). Some residents had to move out of the county or live in substandard housing that lacked running water. Some landlords rented unlivable properties for high prices.

Sources in Tioga, Greene, and Carroll counties reported increased homelessness (Woodrum 2014; Herzenberg, Polson, and Price, 2014; Ward, Polson, and Price, 2014). The Tioga County Department of Human Services reported a four- to five-fold increase in households seeking help with housing (after it started tracking this number in August 2008) (Ward, Polson, and Price, 2014). Tioga County also reported a four-fold increase in the share of Head Start families that were homeless (from 6% in 2010-11 to 24% in 2012-13). Similarly, Greene County saw a jump in the number of children in foster care because of "inadequate housing," from 12 in 2008-09 to 36 in 2012-13. Even in 2009-10, before the boom peaked, Greene County had Pennsylvania's highest rate of homelessness assistance:45 clients per 1,000 residents compared to the state average of seven clients per 1,000 residents.

In Greene County, a local domestic violence organization reported that some clients have found it more difficult to leave abusive situations because of the lack of affordable housing (Herzenberg, Polson, and Price 2014).

Notes on county-level housing data derived from the American Community Survey

The rest of this chapter complements our case studies with quantitative analysis of the impact of drilling on trends in rents, renter incomes, and rental housing affordability.[28]

Our analysis of rental housing and owner-occupied housing relied on data from the American Community Survey (ACS), which has two key limitations.[29]

1. We were unable to identify trends prior to the start of drilling in 2005.[30] For this reason and to increase the size of our samples, we compared changes in housing variables between 2005-07 (before drilling picked up in Ohio and in most of Pennsylvania) and 2010-12.

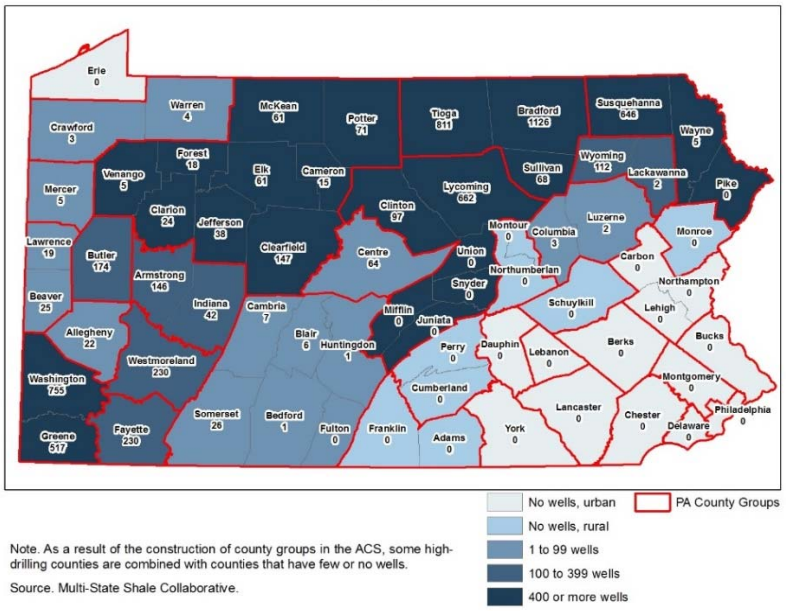
[28] In the Online Technical Appendix we also present data on trends in home prices, homeowner incomes and new housing construction (this includes all new housing construction, whether it is intended for rent or for purchase). Data on home prices and homeowner incomes is available in Chapter 7 Homeowner Incomes. Data for new housing construction is in Chapter 7 Table G15 and Table G16.

[29] We analyzed American Community Survey microdata provided by Steven Ruggles, J. Trent Alexander, Katie Genadek, Ronald Goeken, Matthew B. Schroeder, and Matthew Sobek. Integrated Public Use Microdata Series: Version 5.0 [Machine-readable database]. Minneapolis: University of Minnesota, 2010.

[30] County-level data from the American Community Survey was not available prior to 2005. County-level data from the 2000 Census is available, but differences between the design of the ACS questionnaire and the long form questions on the 2000 Census complicated the interpretation of time trends enough to leave such longer term comparisons for future research.

2. We were restricted to analyzing groups of contiguous counties, as opposed to each individual county.[31] This limitation exacerbated the fact that even county-level data was not as localized as drilling activity and impacts.
    a. In Pennsylvania, as a result of this limitation, putting all six of our high-drilling counties in a single county group would have required also including eight additional rural counties, five of which had no drilling activity (Mifflin, Juniata, Snyder, Union, and Pike). Instead of this, we focused our analysis on smaller county groups, comparing four such groups with one or two of our top drilling counties with other county groups in which less drilling occurred (see Map 7.1 below).[32]

Map 4.1



Note. As a result of the construction of county groups in the ACS, some high-drilling counties are combined with counties that have few or no wells.

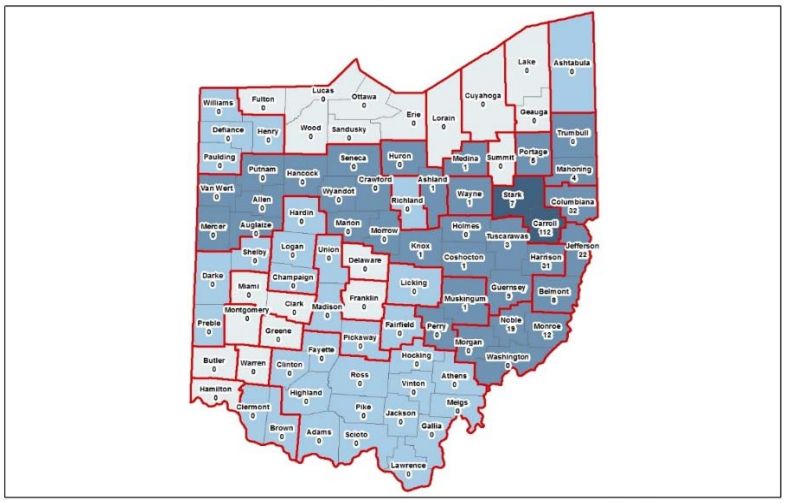
Source. Multi-State Shale Collaborative.

    b. In Ohio (see Map 7.2), observations from Carroll County, which had the most wells, were combined with observations from Stark County (which had just seven wells drilled).

[31] In public use data from the American Community Survey it is not always possible to identify observations from sparsely populated individual counties. Instead, data for these counties are reported in Public Use Microdata Areas (PUMAs), which combine in whole or part smaller counties. For more information see: information https://usa.ipums.org/usa-action/variables/PUMA#description_section.

[32] The sixth high-drilling county, Lycoming, is combined with five other counties: Clinton, Juniata, Mifflin, Snyder, and Union. Its housing industry impacts are, not surprisingly, attenuated, and we do not report the results of this region.

Map 4.2

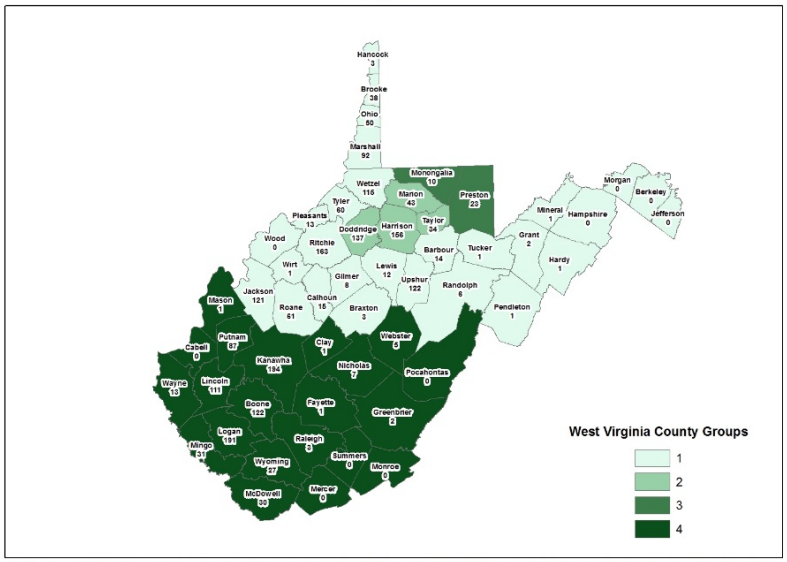


Note. As a result of the construction of county groups in the ACS, some high-drilling counties are combined with counties that have few or no wells.

Source. Multi-State Shale Collaborative

c. Data limitations are most severe in West Virginia, where the ACS includes only four county groups (the state has 55 counties) (Map 7.3). These groups, which do not sharply differentiate drilling and non-drilling regions, also fail to reveal any clear link between drilling and changes in any of the categories analyzed here. Therefore, we do not report the West Virginia data in the text (see the Online Technical Appendix, Chapter 7 West Virginia, for the results of our West Virginia housing analysis).

Map 4.3



Note. As a result of the construction of county groups in the ACS, some high-drilling counties are combined with counties that have few or no wells.

Source. Multi-State Shale Collaborative

Rents by county[33]

In Pennsylvania, from 2005-07 to 2010-12, we find that median rents were up 16.5% in ***Bradford***, Sullivan & ***Tioga*** counties; 9.4% in ***Greene*** and ***Washington counties***; and 13.9% in Pike, ***Susquehanna***, and Wayne counties (the counties highlighted in bold italic are top six drilling counties) (see Table 7.1 below; see the Online Technical Appendix, Appendix D, Table D18 through Table D21 for additional figures). At the 80th percentile, rents increased even more in the two county groups with the most wells.[34]

By contrast, urban and rural county groups with no wells (and most groups with just a few wells) experienced rent increases at the median and the 80th percentile of only 4% to 7% in this five-year span, an increase below the rate of inflation. This reflects the impact of the Great Recession. Drilling did not have as consistent an impact on rents at the 20th percentile.

Table 7.1

Change in rents by amount of drilling in Pennsylvania county/county groups (2012 dollars)

PA county/county group/region	Percent change in rents (2005-2007 to 2010-2012)			Change in wells drilled (2005-2007 minus 2010-2012)
	20th	50th	80th	
Urban*	3.3%	3.4%	6.1%	0
Rural*	6.5%	6.5%	4.1%	0
Bradford, Sullivan & Tioga	4.1%	16.5%	21.6%	1671
Greene & Washington	11.2%	9.4%	13.4%	765
Clinton, Juniata, Lycoming, Mifflin, Snyder, & Union	11.7%	3.8%	7.0%	701
Pike, Susquehanna, & Wayne	4.7%	13.9%	10.7%	523
Cameron, Clarion, Clearfield, Elk, Forest, Jefferson, McKean, Potter, & Venango	2.1%	1.7%	-1.1%	304
Westmoreland	-5.4%	-3.7%	-4.1%	145
Armstrong & Indiana	0.3%	0.7%	3.5%	140
Fayette	1.5%	6.5%	10.7%	137
Butler	-2.2%	-1.5%	2.4%	123
Lackawanna & Wyoming	14.0%	5.4%	4.3%	111

*Rural and urban counties with no wells drilled

[33] In this section we present data on monthly rents for all rental units. Typically, rents are subdivided by the number of bedrooms, but sample size prevents us from doing this. In our summary of trends, we present changes in rents at the 20th percentile (low), 50th percentile (median) and 80th percentile (high).

[34] It's of note that despite these trends, as illustrated in Table G15 and Table G16 (see the Online Technical Appendix, Chapter 7), there was a 26% decline in the number of new housing permits issued in the high-drilling counties from the number issued in 1998-2004. This decline was, however, smaller than the 29% decline observed in rural Pennsylvania counties without wells.

Note. A county or county group is defined as rural if the 2005 population per square mile in that county or county group is below its corresponding statewide total population per square mile of 278.

Source. Multi-State Shale Collaborative based on the American Community Survey microdata provided by Steven Ruggles, J. Trent Alexander, Katie Genadek, Ronald Goeken, Matthew B. Schroeder, and Matthew Sobek. Integrated Public Use Microdata Series: Version 5.0 [Machine-readable database]. Minneapolis: University of Minnesota, 2010.

Overall, given the data limitations, the Pennsylvania data corroborate the case study findings, with differences in rent increases found in drilling county groupings even though virtually all these groupings include either significant urban populations (e.g., Washington and Greene counties) and/or areas with little drilling. Both these data limitations dilute the observed impact of drilling on rents and suggest more detailed data would reveal much greater impacts of drilling on rents.

In Carroll and Stark counties,[35] the only Ohio grouping with more than 100 wells drilled, low and median rents also rose between 2005-07 and 2010-12 by 3.2% and 1.7%, respectively (see Online Technical Appendix, Chapter 7, Table G1). Low and median rents were also up slightly in the remaining Ohio counties with some drilling but not elsewhere in the state.[36]

Renter incomes by county

Rising economic activity would normally be associated with rising incomes in a region. In this section we explore trends in the incomes of renters. In Table 7.2 we present the percent change from 2005-07 to 2010-12 in the household income of renters at the 20th, 50th (median), and 80th percentile for Pennsylvania county groupings, based on the number of wells drilled since 2002 (see the Online Technical Appendix, Chapter 7, Tables G7 through G10 for percent change and levels).

Reflecting the impact of the recession, the median household income of renters was down by 7.6% and 10% in urban and rural portions of Pennsylvania, respectively, that did not see any drilling over this period. In contrast, in the high--drilling regions (***Bradford,*** Sullivan, and ***Tioga counties***), the income of renters at the median and 80th percentile rose about 16.6% and 11.2%, respectively. In the next heaviest-drilling region (which unlike the other groups only high drilling counties), both median and 80th percentile rental incomes in ***Washington and Greene*** counties rose about 20%. Importantly, increases in income in drilling regions were not as consistent at the 20th percentile of the rental income distribution, with a decline in ***Bradford,*** Sullivan, and ***Tioga counties***, for example, that was close to the decline for rural areas with no drilling. If rental rates of properties coming on the market were going up, but the incomes of lower-income renters were not consistently increasing, that could help explain the reports of homelessness problems in our case studies.

[35] Stark County had just seven wells drilled prior to 2013.

[36] Rents were down by between 1.4% and 2.8% over the period analyzed in urban Ohio counties with no wells (Erie, Fulton, Lucas, Ottawa, Sandusky, Wood, Lorain, Cuyahoga, Geauga, Lake, Summit, Delaware, Clark, Miami, Franklin, Greene, Montgomery, Warren, Butler, and Hamilton) and rural counties with no wells (Defiance, Henry, Paulding, Williams, Ashtabula, Champaign, Hardin, Logan, Richland, Madison, Pickaway, Union, Darke, Preble, Shelby, Licking, Fairfield, Adams, Athens, Clinton, Fayette, Gallia, Highland, Hocking, Jackson, Lawrence, Meigs, Pike, Ross, Scioto, Vinton, Brown, and Clermont).

In Carroll and Stark counties, Ohio (see Online Technical Appendix, Chapter 4, Table G7), the median income of renters was down 3% between 2005-07 and 2010-12. Renter incomes were down 6.1% in rural non-drilling counties and 8.7% in urban non-drilling counties.

Table 7.2

Change in the household income of renters in Pennsylvania counties/county groups (2012 dollars)

PA county/county group/region	Percent change in the household incomes of renters (2005-2007 to 2010-2012)			Change in wells drilled (2005-2007 minus 2010-2012)
	20th	50th	80th	
Urban no wells	-0.1%	-10.0%	-1.9%	0
Rural no wells	-6.7%	-7.6%	-4.0%	0
Bradford, Sullivan & Tioga	-5.2%	16.6%	11.2%	1671
Greene & Washington	7.3%	20.0%	20.2%	765
Clinton, Juniata, Lycoming, Mifflin, Snyder, & Union	-10.5%	-5.9%	0.0%	701
Pike, Susquehanna, & Wayne	6.4%	-1.4%	6.0%	523
Cameron, Clarion, Clearfield, Elk, Forest, Jefferson, McKean, Potter, & Venango	-4.5%	-14.5%	-4.9%	304
Westmoreland	-0.4%	0.4%	9.3%	145
Armstrong & Indiana	-9.2%	-6.4%	-1.6%	140
Fayette	-4.0%	5.3%	-1.6%	137
Butler	9.0%	-1.4%	-12.5%	123
Lackawanna & Wyoming	9.4%	-0.1%	7.2%	111

Note. A county or county group is defined as rural if the 2005 population per square mile in that county is below 278.

Source. Multi-State Shale Collaborative based on the American Community Survey microdata provided by Steven Ruggles, J. Trent Alexander, Katie Genadek, Ronald Goeken, Matthew B. Schroeder, and Matthew Sobek. Integrated Public Use Microdata Series: Version 5.0 [Machine-readable database]. Minneapolis: University of Minnesota, 2010.

Rental housing affordability

In Table 7.3 we summarize the percentage of renters paying 30% or more of their income for rent by Pennsylvania drilling county/grouping. In all of the groupings , the number and share of households paying at least 30% of their income in rent climbed from 2005-07 to 2010-12, 3.8% more in ***Bradford***, Sullivan, and ***Tioga counties,*** and 15% more in ***Washington*** and ***Greene counties***. Reflecting the impact of the Great Recession, however, the share of renters paying more than 30% of their income in rents rose even more in the rest of the state: 24% in urban non-drilling areas and 30% in rural non-drilling areas.

In Ohio, the share of households paying at least 30% of their income in rents increased by similar amounts in the drilling counties (Carroll and Stark:17.2%), non-drilling rural counties (15.2%) and non-drilling urban counties (16.8%) (See Online Technical Appendix, Chapter 7, Table G11).

Table 7.3

Percent of renters paying 30% or more of their income in rent for Pennsylvania counties/county groups

PA county/county group/region	Percent of all households	Change in households	Percent change in number of households	Change in wells drilled (2005-2007 minus 2010-2012)
Urban*	42.9%	9,244	29.9%	0
Rural*	51.1%	80,713	23.8%	0
Bradford, Sullivan & Tioga	41.5%	160	3.8%	1671
Greene & Washington	40.8%	1,259	15.0%	765
Clinton, Juniata, Lycoming, Mifflin, Snyder, & Union	41.5%	859	6.6%	701
Pike, Susquehanna, & Wayne	48.5%	1,566	36.9%	523
Cameron, Clarion, Clearfield, Elk, Forest, Jefferson, McKean, Potter, & Venango	41.1%	400	3.2%	304
Westmoreland	42.3%	-5,277	-18.0%	145
Armstrong & Indiana	45.3%	-61	-0.8%	140
Fayette	38.8%	-2,093	-16.7%	137
Butler	42.8%	703	10.6%	123
Lackawanna & Wyoming	39.0%	-89	-0.7%	111

*Rural and urban counties with no wells drilled

Note. A county or county group is defined as rural if the 2005 population per square mile in that county is below 278.

Source. Multi-State Shale Collaborative based on the American Community Survey microdata provided by Steven Ruggles, J. Trent Alexander, Katie Genadek, Ronald Goeken, Matthew B. Schroeder, and Matthew Sobek. Integrated Public Use Microdata Series: Version 5.0 [Machine-readable database]. Minneapolis: University of Minnesota, 2010.

Panel Regression on Rents, Renter Income and Rental Housing Affordability

As discussed in the beginning of this chapter, our data set on housing is drawn from the American Community Survey (ACS) and thus, unlike for our previous analysis, we lack a period prior to the start of drilling in that we are comparing rents, renter incomes and rental housing affordability in West Virginia, Pennsylvania and Ohio in two three-year periods 2005-07 and 2010-12. Furthermore, due to the aggregation of counties in the ACS, we have fewer observations than when analyzing data with observations for each county in the region.

We examined each of our housing variables of interest (expressed as logs) using a fixed effects panel regression and only three indicator variables as independent variables. Our indicator variables were set equal to 1 in 2010-12 in county groups that had high activity (400 or more wells drilled over the period), medium activity (100 to 399 wells drilled over the period), low activity (1 to 99 wells drilled over the

period) and 0 otherwise (the reference group thus includes counties without wells drilled in both periods and all drilling counties in 2005-07).[37] Table 7.4 reports the coefficients for each level of drilling activity for median rents, 20th percentile rents, and 80th percentile rents. In high-drilling counties the coefficient is statistically significant, with median rents up 10%, 20th percentile rents up 7.6%, and 80th percentile rents up 12.3%. None of the coefficients for medium- or low-drilling counties was statistically significant.

Table 7.4

Median, 20th percentile, and 80th percentile rents in West Virginia, Pennsylvania and Ohio by high-, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of median rents	Dependent variable = natural log of 20th percentile rents	Dependent variable = natural log of 80th percentile rents
	b/se	b/se	b/se
High-drilling	0.102***	0.076***	0.123***
	(0.022)	(0.017)	(0.024)
Medium-drilling	0.015	0.027	0.011
	(0.012)	(0.017)	(0.015)
Low-drilling	0.012	0.008	0.019
	(0.013)	(0.014)	(0.016)
Constant	6.545***	6.201***	6.843***
	(0.002)	(0.002)	(0.002)
R-sqr-overall	0.015	0.035	0.005
N	144	144	144

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels.
Standard error estimates are robust to disturbances being heteroscedastic.

With respect to renter incomes at the median, 20th percentile, and 80th percentile (expressed in logs) in high-drilling counties, the coefficient for median renter incomes and 20th percentile renter incomes is not statistically significant (Table 7.5). In contrast, the coefficient for 80th percentile renter incomes was significant, indicating that these renters' incomes were up 8.7% in the high-drilling counties. The coefficients for renter incomes in medium-drilling counties were not statistically significant. In low-drilling counties/county groups, the coefficient on median and 20th percentile renter incomes was both significant and negative, indicating a decline in median incomes of 5.6%, and in 20th percentile incomes of 4%.

[37] The results for rents, renter income and housing affordability do not represent a full accounting of the factors that explain differences between counties in these variables. These results provide a limited test of the association among drilling, rising rents, and declining housing affordability. Researchers interested in further exploring the strength of these relationships can find this dataset in the Online Technical Appendix, Chapter 7, AppendixG.dta (stata).

Table 7.5

Median, 20th percentile and 80th percentile renter incomes in West Virginia, Pennsylvania and Ohio by high-, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of median renter income	Dependent variable = natural log of 20th percentile renter income	Dependent variable = natural log of 80th percentile renter income
	b/se	b/se	b/se
High-drilling	-0.008	0.065	0.087**
	(0.039)	(0.053)	(0.034)
Medium-drilling	-0.011	-0.044**	-0.012
	(0.021)	(0.021)	(0.027)
Low-drilling	-0.056*	-0.040**	0.019
	(0.031)	(0.019)	(0.018)
Constant	9.373***	10.205***	10.881***
	(0.004)	(0.003)	(0.003)
R-sqr-overall	0.082	0.079	0.003
N	144	144	144

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels. Standard error estimates are robust to disturbances being heteroscedastic.

Given evidence that rents were up, but renter incomes were not in high-drilling counties over the period, it was not surprising that when examining the number of renters paying at least 30% of their income in rent we found a statistically significant and positive coefficient (Table 7.6). Specifically, we found a 13.9% increase in the number of renters paying at least 30% of their income in rent.

Table 7.6

Number of renters paying at least 30% of their income in rent in West Virginia, Pennsylvania and Ohio by high-, medium- and low-drilling activity

Independent variables	Dependent variable = natural log of number of household paying 30% or more of their income in rent
	b/se
High activity	0.139**
	(0.055)
Medium activity	0.025
	(0.048)
Low activity	0.137***
	(0.030)
Constant	9.404***
	(0.005)
R-sqr-overall	0.008
N	144

Notes. *, ** and *** indicate significance at the 10, 5 and 1 percent levels. Standard error estimates are robust to disturbances being heteroscedastic.

Chapter 8: Other Pennsylvania Specific Impacts

This chapter considers four additional human service impacts identified in our case studies but for which no standard data source exists across multiple states: emergency room visits, early intervention services for children with developmental delays, foster care, and prison populations. Given our reliance on state-specific data, we restricted our analysis to Pennsylvania: This made our task more manageable. Our three-state analysis of other social impacts also consistently documented that most impacts occurred in the six Pennsylvania counties with the most wells drilled from 2005 to 2012. In this chapter, the link we found between drilling and demand for these additional human/social services was not a tight one. Whether that would change with better data remains an open question.

Emergency Room Visits

Some research has explored the link between increased gas drilling and emergency room visits. Hessert (2012) found some increase in emergency room visits in the Marcellus Shale region, although researchers were unsure how much of this was due to gas drilling. Jersey Shore Hospital in Lycoming County, PA, reported an operating budget deficit for the first time in 2013, which it attributed to uncompensated care costs for uninsured sub-contractors in the gas industry (*Republican Herald* 2013). The county government in Sublette County, WY, had substantial fiscal impacts due to needed expansion of medical clinics in the region to deal with the incoming population connected to the gas industry (Ecosystems Research Group 2009). Ecosystems Research Group and Headwaters (2008) also found an increase in patients without health insurance, which coincided with more gas drilling in the area that could lead to increased emergency room visits (although these researchers did not document such a connection).

Our case studies found increases in emergency room visits in Tioga and Greene counties, PA. In Tioga County, PA, Soldiers and Sailors Memorial Hospital saw an increase in emergency room visits between 2006-07 and 2011-12, with the largest increase occurring between 2010-11 and 2011-12, during the height of the gas boom. The hospital has also seen some uptick in uncompensated care coinciding with the gas boom (Ward, Polson, and Price 2014). In Greene County, the Southwest Regional Medical Center saw a sharp rise in emergency room visits between 2005-06 and 2010-11, coinciding with increased drilling (Herzenberg, Polson, and Price 2014).

Looking at Pennsylvania as a whole, no strong correlation exists between increased gas drilling and increases in emergency room visits. For example, in counties with 400 or more wells, ER visits increased 12%, compared to counties with no drilling in which visits increased by 11% (Table 8.1).

Table 8.1

ER visits in Pennsylvania by number of wells drilled

Wells drilled/region	ER visits per 100,000 people in 2012	2001 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
400 or more wells	54618	2543	6%	6028	12%	4517
100 to 399 wells	38483	3478	10%	-899	-2%	1039
1 to 99 wells	53682	4080	9%	4634	9%	695
No wells, rural	43993	3288	9%	4275	11%	0
No wells, urban	46375	4663	13%	5305	13%	0

Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

Looking at individual counties, four of the six high-drilling counties saw increases in emergency room visits of more than 10%, with Greene County leading the way (66% increase between 2005 and 2012). The relationship between the level of drilling and the increase in emergency room visits, however, was not a consistent one: Two counties that had 230 wells drilled each experienced small decreases in visits, and two counties with between 100 and 200 wells saw decreases of more than 10% (Butler and Wyoming (Table 8.2).

Table 8.2

ER visits in counties with 100 or more wells drilled

Wells drilled/region	ER visits per 100,000 people in 2012	2001 to 2005		2005 to 2012		Total wells drilled 2005 to 2012
		Change	Percent change	Change	Percent change	
Pennsylvania, Urban*	46375	4663	13%	5305	13%	0
Pennsylvania, Rural*	43993	3288	9%	4275	11%	0
Bradford	78005	1502	2%	7846	11%	1126
Tioga	42690	1022	3%	6866	19%	811
Washington	50158	1996	5%	5630	13%	755
Lycoming	64834	5294	9%	1610	3%	662
Susquehanna	19831	1555	9%	53	0%	646
Greene	61402	2624	8%	24317	66%	517
Westmoreland	51046	5892	12%	-3347	-6%	230
Fayette	33254	2259	7%	-474	-1%	230
Butler	25475	2127	7%	-5314	-17%	174
Clearfield	71977	7567	15%	12687	21%	147
Armstrong	38246	4861	15%	1552	4%	146
Wyoming	34880	3305	9%	-5905	-14%	112

*limited to counties with no wells drilled between 2002 and 2012

Source. Multi-State Shale Collaborative based on Pennsylvania State Police and Bureau of Economic Analysis data.

Looking forward, better data could help more definitively settle whether drilling contributes to ER visits and increases in the costs of health care.

Early Intervention

Case Study Findings

Early intervention services are designed to serve children with developmental delays or disabilities from birth. to school age. . Our case study research revealed potential links between drilling and an increased need for early intervention services for kids 0-5, and special education for school-age kids. To our knowledge, such a link has not been reported previously in the research literature.

In Greene County, Pennsylvania, human service staff reported that a November 2012 assessment found that one-quarter of the children receiving early intervention services were the children of drillers. Human service personnel did not offer an explanation for this (Herzenberg, Polson, and Price 2014).

In Tioga County, the Southern Tioga School District experienced an increase in students requiring special education services, including emotional and learning supports. The superintendent reported the district had 320 special needs students out of a total enrollment of 2,100 students before drilling began. After the gas boom, the number of special needs students increased to 404, even though the student population had decreased to 1,900 (Ward, Polson, Price 2014).

Quantitative Analysis of Demand for Early Intervention Services

We analyzed early intervention data collected from the Pennsylvania Office of Child Development and Early Learning by the Kids Count initiative. These data include early intervention services for infants/toddlers (0-2) and preschool-aged kids (3-5).

Table 8.3 shows early intervention enrollment (rates per 100,000 people) over time in counties with and without drilling. Early intervention services grew across the state between 2004-2006 and 2010-2012. Services in drilling counties (both those with more than 400 wells, and those with 100-399 wells) grew at more than twice the rate of services in rural counties with no wells. For example, counties with 400 or more wells saw early intervention services increase by 32%, compared to a 15% increase in rural non-drilling counties. Except for this lower increase in rural non-drilling areas, however, all other parts of the state experienced similar increases in early intervention services, independent of the amount of drilling. It could be possible that some factor independent of drilling was driving increases across all of these areas, but that this factor is less influential in rural non-drilling counties. It could also be that drilling was driving increases in rural areas with wells, and a different causal factor was driving increases in urban areas.

Table 8.3

Early intervention rate (early interventions per 100,000 people) in Pennsylvania by the number of wells drilled

Wells drilled/region	2004-06	2007-09	2010-12	Percent Change 2004-06 to 2010-12	Total wells drilled
Pennsylvania, 400 or more wells	443	551	583	32%	4517
Pennsylvania, 100 to 399 wells	458	539	616	35%	1039
Pennsylvania, 1 to 99 wells	497	575	626	26%	695
Pennsylvania, No wells, rural	467	520	538	15%	0
Pennsylvania, No wells, urban	528	620	705	34%	0

Source. Multi-State Shale Collaborative based on Pennsylvania Office of Child Development and Early Learning.

What link might exist between increased early intervention services and drilling requires more research. Are gas drillers' families more likely to need early intervention services? If so, why? Are pregnant women and young children in the area impacted by environmental factors related to increased gas drilling that lead to disabilities, developmental delays, etc.? One study reported that specific chemicals used in unconventional gas drilling can affect the endocrine system (Song 2012). The lead researcher reported that endocrine-disrupting chemicals have been linked to a variety of health issues – obesity, diabetes, fetal development problems and infertility. Babies and young children are especially vulnerable – "during fetal development, if you don't have the right level of hormones in the thyroid, you can have severe mental retardation." Another study identified 649 chemicals used during gas drilling, of which 130 could affect the endocrine system (Vandenberg et al. 2012).

Foster Care

Our case study research found that in Greene County, PA, the number of kids going into foster care due to inadequate housing more than doubled during the gas boom between 2008-09 and 2009-10 (from 15% to 36%) and has remained nearly as high since. Increased cost of foster care has put a financial strain on the Greene County Human Services Department (Herzenberg, Polson, and Price 2014).

Analysis of foster care data across all Pennsylvania counties, however, does not show a consistent relationship between children entering foster care and drilling activity. Greene County is one of only two top drilling counties that saw an increase in foster care rates between 2008 and 2011 (Table 8.4 and Table 8.5). Between 2008 and 2012, the foster care rate grew by 8% in Greene County and by 4% in Fayette County. In every other Pennsylvania county with 100 or more wells drilled, the number of kids in foster care decreased during this time period. And in rural counties with no drilling the number decreased by 19%. Analysis by county groupings based on the amount of drilling also shows no relationship between drilling and demand for foster care.

Table 8.4

Foster care rates (foster care cases per 100,000 people) in Pennsylvania counties with 100 or more wells drilled

Wells drilled/region	Total foster care rates reported per 100,000 people				Change 2008 to 2011	Percent change 2008 to 2011	Total wells drilled
	2008	2009	2010	2011			
Pennsylvania, Urban*	268	235	198	177	-91	-34%	0
Pennsylvania, Rural*	197	177	178	159	-38	-19%	0
Bradford, PA	393	332	335	248	-146	-37%	1126
Tioga, PA	336	289	236	252	-84	-25%	811
Washington, PA	284	254	219	201	-83	-29%	755
Lycoming, PA	187	157	109	88	-99	-53%	662
Susquehanna, PA	191	161	189	174	-17	-9%	646
Greene, PA	202	188	184	219	16	8%	517
Fayette, PA	116	104	111	120	4	4%	230
Westmoreland, PA	198	154	138	198	-1	0%	230
Butler, PA	194	178	152	116	-77	-40%	174
Clearfield, PA	226	189	165	195	-31	-14%	147
Armstrong, PA	126	114	116	100	-26	-21%	146
Wyoming, PA	173	134	106	92	-81	-47%	112

*Limited to counties with no wells drilled between 2002 and 2012

Source. Multi-State Shale Collaborative based on Kids Count Data and Bureau of Economic Analysis data.

Table 8.5

Total foster care rates in Pennsylvania by the number of wells drilled

Wells drilled/region	Total foster care rates reported per 100,000 people				Change 2008 to 2011	Percent change 2008 to 2011	Total wells drilled
	2008	2009	2010	2011			
Pennsylvania, 400 or more wells	265	232	204	184	-81	-31%	4517
Pennsylvania, 100 to 399 wells	159	137	129	136	-22	-14%	1039
Pennsylvania, 1 to 99 wells	250	218	192	187	-63	-25%	695
Pennsylvania, Rural*	197	177	178	159	-38	-19%	0
Pennsylvania, Urban*	268	235	198	177	-91	-34%	0

*Limited to counties with no wells drilled between 2002 and 2012

Source. Multi-State Shale Collaborative based on Kids Count Data and Bureau of Economic Analysis data.

In light of our case study findings in Greene County, we also looked specifically at the impact of drilling on children placed into foster care due to inadequate housing. Only three of 12 counties with more than 100 wells drilled saw increases in foster care placements due to inadequate housing: Westmoreland (21%), Greene County (129%), and Armstrong County (272%). All other heavily drilled counties saw a decrease in foster care rates due to inadequate housing between 2008 and 2012.

Chapter 9: Conclusion

What is the takeaway from our analysis of data on human and social impacts of drilling and our prior case studies?

Both our case studies and our statistical analysis of employment revealed some positive employment and income benefits of shale development in high-drilling counties, especially in Greene County, Pennsylvania.

This report reveals the other side of the coin: The high-drilling counties, measured by number of wells and by industry and total employment impacts, also experienced negative community impacts, such as higher rates of crime, STDs, and traffic fatalities, and less affordable housing.

Our findings are consistent with the qualitative picture of drilling impacts from case studies in Wyoming and other drilling states. High levels of drilling lead to an increase in employment, some of it as a result of an influx of transient out-of-state workers making higher-than-average wages. Drilling activity itself, out-of-state workers, and the increase in income and valuable (and portable) equipment and materials on drilling sites, contribute to increases in crime, traffic accidents, STD rate, and rents. Some of these impacts may have been mitigated in the Marcellus and Utica Shale regions by the lack of apparent increase in overall population; this may reflect, in addition to data limitations, the fact that rural drilling counties in Pennsylvania, West Virginia, and Ohio are more densely populated than parts of the west. As a result, drilling counties in the east may have more pre-existing infrastructure and social services than their counterparts in Wyoming and North Dakota. Regardless, our research indicates that Marcellus and Utica Shale communities in which the scale of shale development is sufficient to move the needle on total employment and income are also communities likely to be faced with social challenges as a result of the drilling intensity. Communities with shale deposits where drilling has not yet occurred should understand this trade-off so that they can weigh their options in an informed way and prepare for the social impacts if drilling does expand to them.

References

Anderson, B., & Theodori, G. 2009. "Local Leaders' Perceptions of Energy Development in the Barnett Shale." Southern Rural Sociological Association.

Begos, Kevin. 2014. "AP Impact: Deadly side effect to fracking boom." Associated Press, May 5. Accessed on 6/25/14 at http://bigstory.ap.org/article/ap-impact-deadly-side-effect-fracking-boom-0.

Boyd, S., Gordon, R., Leeman, K., Pascal, V., Poole, C., Porter, S., and Stewart, R. 2013. The Impact of Horizontal Shale Well Development on Housing. Athens, OH: Voinovich School of Leadership and Public Affairs at Ohio University.

Census Bureau. 2013. "Oil and Gas Boom Driving Population Growth in the Great Plains, Census Bureau Estimates Show". http://www.census.gov/newsroom/press-releases/2013/cb13-46.html

Coolidge, Erick. 2011. "Testimony on Community Impacts from Marcellus Shale Drilling." Senate Republican Policy Committee. January 26, 2011.

Covey, Staci. 2011. "Local Experiences Related to the Marcellus Shale Industry." Guthrie. May 10

Eligon, John. 2013. "An Oil Boom takes a toll on health care." New York Times, January 27, 2013. Accessed on 6-24-14 at http://www.nytimes.com/2013/01/28/us/boom-in-north-dakota-weighs-heavily-on-health-care.html?pagewanted=all&_r=0

Ellis, Blake. 2011. "Crime turns oil boomtown into Wild West." CNN Money, October 26, 2011. Accessed on 6/24/14 at http://money.cnn.com/2011/10/26/pf/America_boomtown_crime/.

Ecosystems Research Group. 2008. Sublette County Socieoeconomic Impact Study: Phase I Final Report. Sublette County Commissioners.

Ecosystems Research Group. 2009. "Sublette County Socieoeconomic Impact Study: Phase II Final Report." Sublette County Commissioners.

Food and Water Watch. 2013. "The Social Costs of Fracking: A Pennsylvania Case Study." Food and Water Watch: Washington DC.

Gopalakrishnan, S., & Klaiber, H. A. 2012. "Is The Shale Boom a Bust for Nearby Residents? Evidence from Housing Values in Pennsylvania." Ohio State University Department of Agricultural, Environmental, and Development Economics.

Headwaters Economics. 2008. "Impacts of Energy Development in Colorado: With a Case Study of Mesa and Garfield Counties." Headwaters Economics: Bozeman, Montana.

Headwaters Economics. 2009. "Impacts of Energy Development in Wyoming: With a Case Study of Sweetwater County."

Herzenberg, Stephen, Diana Polson, Mark Price. "Measuring the Costs and Benefits of Natural Gas Development in Greene County, Pennsylvania: A Case Study." Multistate Shale Research Collaborative. April 2014.

Hessert "The Marcellus Shale Boom: How Has It Affected Health Care in Rural Pennsylvania." Pennsylvania Office of Rural Health. Pennsylvania Rural Health, Fall 2012.

Jacquet, Jeffrey. 2005. "Index Crimes, Arrests, and Incidents in Sublette County 1995 to 2004." Sublette County, Wyoming, Dec. 2005.

Jacquet, J. 2009. "Energy Boomtowns & Natural Gas: Implications for Marcellus Shale Local Governments & Rural Communities". Northeast Regional Center for Rural Development.

Levy, Marc. 2011. "Towns see crime, carousing surge amid gas boom: Boom in oil and gas drilling brings surge in carousing and crime; small-town police outmanned." Associated Press. October 26, 2011. Accessed on 6/24/14 at http://finance.yahoo.com/news/Towns-see-crime-carousing-apf-2993474936.html.

Mauro, F., Wood, M., Mattingly, M., Price, M., Herzenberg, S., & Ward, S. (2013). *Exaggerating the Employment Impacts of Shale Drilling: How and Why*. Multi-State Shale Research Collaborative. http://www.multistateshale.org/shale-employment-report

Mauro, Frank. (2014). Exaggerating the Potential Income Impacts of Shale Drilling in Upstate New York, Multi-State Shale Research Collaborative and Fiscal Policy Institute. Forthcoming.

Muehlenbachs, L., Spiller, E., & Timmins, C. 2012. Shale Gas Development and Property Values: Differences Across Drinking

Water Sources. National Bureau of Economic Research Working paper 18390

Murray, S., & Ooms, T., 2008. "The Impact of Marcellus Shale in Northeastern Pennsylvania with an Emphasis on Charities, Crime, and Poverty." Joint Urban Studies Center. May 2008.

O'Leary, Sean. 2014. "Impacts of Gas Drilling in Wetzel County." West Virginia Center on Budget and Policy. April 2014.

Redifer, John, Georgann Jouflas, Thea Chase, Susanna Morris. 2007. "Socioeconomic Impacts of Growth." "Mesa State College Natural Resource and Land Policy Institute. September 2007.

Republican Herald. 2013. "Shale workers extract care." Republican Herald, January 12, 2013. Accessed on 4/7/14 at http://republicanherald.com/opinion/shale-workers-extract-care-1.1428409

Schaeffer, Lisa. 2011. "Testimony on Marcellus Shale Drilling." County Commissioners Association of Pennsylvania. Presented

Schafft, K. A., & Glenna, L.L. 2012. "Marcellus Shale Gas Development: What Does It

Troxell, Edward C. 2011. "Testimony on Impacts of Marcellus Shale Gas Development on Local Governments." Pennsylvania

State Association of Boroughs. Presented before the Senate Majority Policy Committee on 1/26/11.

Vaughan, Vicky. 2012. “Boom takes toll on health care, social services.” My San Antonio, July 18, 2012. Accessed on 6/24/14 at http://www.mysanantonio.com/news/local_news/article/Boom-takes-toll-on-health-care-social-services-3717774.php#ixzz21BqLWxqN.

Ward, Sharon, Diana Polson, and Mark Price. 2014. “Measuring the Costs and Benefits of Natural Gas Development in Tioga County, Pennsylvania: A Case Study.” Multistate Shale Research Collaborative. April 2014.

Woodrum, Amanda. 2014. “Fracking in Carroll County, Ohio: An Impact Assessment.” Policy Matters Ohio. April 2014.

pennsylvania
DEPARTMENT OF ENVIRONMENTAL PROTECTION

2015 Natural Gas Emissions Inventory by Source Type (Tons per Year)

2015 Natural Gas Emissions	Total Emissions (Tons)															
Source Category	CO	NOx	PM-10	PM-2.5	SOx	VOC	Benzene	Ethyl Benzene	Formal dehyde	n-Hexane	Toluene	Xylenes	2,2,4-Trimethyl pentane	Carbon Dioxide	Methane	Nitrous Oxide
BLOWDOWN VENTS	10	4	0	0	0	359	0.1	0.1	0	3.2	0.2	0.5	0	8,554	21,136	0
COMPLETIONS	2,510	8,353	245	220	123	327	3.8	0.9	3	1.2	1.4	1	0	584,154	6,237	32.9
DEHYDRATORS	230	77	2	2	0	459	6.2	3.4	0	0.7	12.9	21.2	0.7	113,799	17,233	142.3
DRILL RIGS	1,859	4,382	135	128	32	238	1.8	0	10.5	0.3	0.7	0.5	0.1	340,431	20	6.4
ENGINES	2,848	5,929	208	206	19	1,416	14.6	0.6	382.3	1.3	8.5	3.6	4.9	4,129,078	9,691	24
FUGITIVES	27	6	0	0	0	1,365	1.5	0.2	0	26.1	5	7.9	0.8	5,105	19,810	0
HEATERS	1,141	1,310	81	77	7	134	0.6	0.3	0.9	14.3	3.2	6.8	0.2	1,508,403	1,087	15.2
PIGGING	0	0	0	0	0	52	0	0	0		0	0	0	328	997	0
PUMPS	0	0	0	0	0	1,019	0.4	0.4	0	34.6	1.6	3.7	0.5	126	32,105	15
TANKS	63	32	1	1	0	1,042	0.4	0.1	0	22.4	0.8	0.6	0	9,888	3,812	38.5
Emission Totals	**8,688**	**20,093**	**672**	**634**	**181**	**6,411**	**29**	**6**	**397**	**104**	**34**	**46**	**7**	**6,699,866**	**112,128**	**274**

Stationary Engines: A stationary engine is an engine whose framework does not move. It is normally used to drive a piece of immobile equipment such as a pump or compressor. They may be powered by steam, oil-burning or internal combustion engines. They come in a wide variety of sizes and are used for a wide variety of purposes.

Heaters and Reboilers

Heaters: Heaters are enclosed devices that use a controlled flame. Its primary purpose is to transfer heat indirectly to a process material (liquid, gas, or solid) or to a heat transfer material for use in a process unit, instead of generating steam.

Reboilers: Reboilers are heat exchangers typically used to provide heat to the bottom of industrial distillation columns. They boil liquid from the bottom of a distillation column to generate vapors which are returned to the column to drive the distillation separation.

Tanks/Vessels: These types of units are constructed primarily of nonearthen materials (such as wood, concrete, steel, fiberglass, or plastic) which provide structural support and are designed to contain liquids or other materials. They include storage tanks, pressurized vessels, impoundments, separators and other similar units.

Dehydrators: A dehydrator is a device in which an absorbent directly contacts a natural gas stream and absorbs water in a contact tower or absorption column (absorber). They are used for removal of water vapor from natural gas wellstreams.

Pneumatic Devices: Pneumatic devices are automated instruments used for maintaining liquid levels, pressure, and temperature at wells and gas processing plants. These controllers often are powered by high-pressure natural gas and may release gas with every valve movement, or continuously as part of their normal operations.

Venting and Blowdowns

Venting: The process of reducing gas pressure by means of releasing pressure to the atmosphere.

Blowdowns: A blowdown is a type of venting which releases pressurized natural gas, containing mostly methane, from pipelines or facilities by venting it to the atmosphere. Blowdowns occur during normal maintenance procedures or emergency shutdowns.

Drill Rigs: A drilling unit that is not permanently fixed and its associated machinery.

Completions and Workovers

Completions: A completions is a process that allows for the flowback of petroleum or natural gas from newly drilled wells to expel drilling and reservoir fluids and tests the reservoir flow characteristics, which may vent produced hydrocarbons to the atmosphere via an open pit or tank. The completion process may involve selectively perforating the well casing at the depth of discrete producing zones and installing down-hole equipment. The completion process may take anywhere from a few days to several weeks to accomplish.

Workovers: Producing oil and natural gas wells occasionally requires major repairs or modifications, called "workovers." Workover services are carried out with the same type of rig used to perform maintenance services, although the rig often is outfitted with specialized equipment including rotary drilling equipment, mud pumps, mud tanks and blowout preventers. A workover may last anywhere from a few days to several weeks to accomplish.

Fugitives: Those emissions which could not reasonably pass through a stack, vent, or other functionally equivalent opening, including emissions leaks from connectors, flanges, open end lines, pump seals, valves, etc.

Pigging: Emissions rendered from the execution of pipeline maintenance that involves the use of devices known as pigs, which clean pipelines and are capable of performing pipeline inspections. The pigging process is done without necessarily interfering with the flow of product in the pipe.

HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Epidemiology. 2016 March ; 27(2): 163–172. doi:10.1097/EDE.0000000000000387.

Unconventional natural gas development and birth outcomes in Pennsylvania, USA

Joan A. Casey[a,e], **David A. Savitz**[d], **Sara G. Rasmussen**[a], **Elizabeth L. Ogburn**[b], **Jonathan Pollak**[a], **Dione G. Mercer**[f], and **Brian S. Schwartz**[a,c,f]

[a] Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[b] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[c] Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

[d] Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island, USA and Department of Obstetrics and Gynecology, Alpert School of Medicine, Brown University, Providence, Rhode Island, USA

[e] Robert Wood Johnson Foundation Health and Society Scholars Program, UC San Francisco and UC Berkeley, California, USA

[f] Center for Health Research, Geisinger Health System, Danville, Pennsylvania, USA

Abstract

Background—Unconventional natural gas development has expanded rapidly. In Pennsylvania the number of producing wells increased from zero in 2005 to 3689 in 2013. To our knowledge, no prior publications have focused on unconventional natural gas development and birth outcomes.

Methods—We performed a retrospective cohort study using electronic health record data on 9384 mothers linked to 10946 neonates in the Geisinger Health System from January 2009-January 2013. We estimated cumulative exposure to unconventional natural gas development activity with an inverse-distance squared model that incorporated distance to the mother's home; dates and durations of well pad development, drilling, and hydraulic fracturing; and production volume during the pregnancy. We used multilevel linear and logistic regression models to examine associations between activity index quartile and term birth weight, preterm birth, low 5 minute Apgar score and small size for gestational age, while controlling for potential confounding variables.

Results—In adjusted models, there was an association between unconventional natural gas development activity and preterm birth that increased across quartiles, with a fourth quartile odds ratio of 1.4 (95% CI: 1.0-1.9). There were no associations of activity with Apgar score, small for

Corresponding author: Brian S. Schwartz, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Room W7041, Baltimore, MD, 21205. bschwar1@jhu.edu..

Conflicts of Interest We declare that we have no conflicts of interest.

gestational age, or term birth weight (after adjustment for year). In a *post-hoc* analysis, there was an association with physician-recorded high-risk pregnancy identified from the problem list (fourth vs. first quartile, 1.3 [95% CI: 1.1-1.7]).

Conclusion—Prenatal residential exposure to unconventional natural gas development activity was associated with two pregnancy outcomes, adding to evidence that unconventional natural gas development may impact health.

INTRODUCTION

The last decade has seen rapid development of unconventional natural gas resources worldwide; the International Energy Agency reports that 18% of global gas production now comes from unconventional sources. The steepest increases have occurred in the United States (U.S.) and in particular in the Marcellus shale in Pennsylvania. From 2006 to 2013, annual conventional gas production in Pennsylvania was stable at around 5.7 billion cubic meters (bcm); prior to 2009, unconventional production was less than 10 bcm, and then production increased rapidly to 3048 bcm in 2013.

Unconventional natural gas development is a large-scale multi-stage process.[1-4] Developers use diesel equipment to clear land for well pads, transport materials, and drill multiple wells per pad. Directional drilling, first vertically and then horizontally, and hydraulic fracturing ("fracking") differentiate this process from conventional development. Hydraulic fracturing involves injecting millions of liters of water mixed with sand and chemicals into the borehole causing fractures in the shale formation. Fracturing fluids, flowback and produced water, and natural gas then flow to the surface for collection and use. Gas is sometimes flared, releasing pollutants. Wells produce natural gas at high rates for the first year, with a rapid decline over the first three years.

Prior studies have demonstrated environmental impacts from the various stages of unconventional natural gas development including pollution of air,[5-9] surface water,[10] groundwater,[11,12] and soil as recently reviewed.[1-3] Truck traffic, drilling, hydraulic fracturing, and production can generate diesel particulate matter, fine particulate matter ($PM_{2.5}$), methane, NO_x, and volatile organic compounds, which are also ozone precursors.[5-7,13] Some of these pollutants, most consistently $PM_{2.5}$, NO_x, SO_x, and ozone, have been associated with adverse birth outcomes including low or reduced birth weight14-16 and preterm birth.14,17,18 $PM_{2.5}$ and ozone are regional air pollutants, so women living long distances from unconventional natural gas development could experience effects.

Expectant mothers could also be exposed to water pollution from unconventional natural gas development. A recent study identified 2-n-butoxyethanol – a chemical found in flowback water from the process, which might be a general indicator of its contamination – in household well water in Pennsylvania.[12] In addition, people living in communities near unconventional natural gas development commonly report symptoms (e.g., upper respiratory symptoms, headaches), and may experience psychosocial stressors from rapid industrial development, increased motor vehicle traffic, potential influences on environmental radon pathways, noise, and infusion of short-term workers.[1,4,19-23] Some of these exposures have

also been linked to negative birth outcomes.[24,25] A recent study in Colorado reported that density of and proximity to natural gas wells were associated with congenital heart and neural tube defects, but not with birth weight or preterm birth.[26] This study did not distinguish between conventional and unconventional wells, and mainly described associations with conventional wells since the Energy Information Agency estimated that only 25% of natural gas produced in Colorado in 2009 came from unconventional sources. There is an unpublished study that found mothers living near unconventional natural gas development in Pennsylvania gave birth to infants with increased prevalence of low birth weight, low Apgar scores, and small for gestational age.[27]

In this study, we exploited the geographic overlap of the Geisinger Health System and unconventional natural gas development in Pennsylvania to conduct a retrospective cohort study by linking electronic health record data to estimates of exposure to the activities during pregnancy. Despite calls for health studies,[28,29] to our knowledge there is only one published population-based study focused on unconventional natural gas development and objective health outcomes.[30] We evaluated associations between an index of unconventional natural gas development activity and four birth outcomes.

METHODS

Study area and participants

The Geisinger Health System serves a primary market of approximately 40 counties in central and northeast Pennsylvania, a region with a 2010 population of over 4 million residing in over 1200 communities defined as townships, boroughs, and census tracts in cities.[31] Patients with a Geisinger primary care provider are representative of the general population based on age, sex, race/ethnicity, and rural residence.[32] Neonates were delivered at two hospitals, Geisinger Medical Center in Danville, which has a Level IV neonatal intensive care unit (NICU), and Geisinger Wyoming Valley in Wilkes-Barre, which has a Level II NICU. The Institutional Review Board at the Geisinger Health System reviewed and approved the study.

Singleton births to women who delivered at Geisinger between 2006 and January 2013 were eligible for inclusion. We identified births and deliveries using International Classification of Diseases, Ninth Revision codes (i.e., V27.x, V30.x) in mother and neonate electronic health records. We used medical record numbers and other data found in the electronic health record to link mothers with their neonates. We excluded those whom we could not match, stillbirths, and neonates with serious birth defects, birth weights < 500g or gestational ages < 22 weeks. Only mother's 2013 address was available from the electronic health record, so we assumed they lived at the same address during pregnancy. We geocoded women's residences using ArcGIS 10.2[31] and excluded those who did not reside in Pennsylvania or whose address we were unable to geocode. We evaluated our assumption of mother's residential stability by comparing addresses in two Geisinger Health System datasets, 39 months apart (one from 2010 and the other from 2013), among 333,322 patients in both datasets. Due to strong collinearity between the unconventional natural gas development exposure metric and calendar year, we also excluded births prior to 2009 when little such activity had taken place in the study region.

Birth outcomes

We extracted data from electronic health record files including labor and delivery notes and a separate labor and delivery database maintained continuously by nursing personnel. The clinician recorded gestational age as part of routine care based on patient-reported last menstrual period and 20 week ultrasound. We estimated the first day of pregnancy from gestational age. We studied four birth outcomes: term (≥ 37 week) birth weight, preterm birth (< 37 weeks gestation), low 5 minute Apgar score (< 7), and small for gestational age; we isolated moderate to late preterm birth (32-36 weeks gestation) in a sensitivity analysis. Infants with low 5 minute Apgar scores often require respiratory support and have poorer future academic achievement.[33] Small for gestational age was defined as less than the sex-specific 10th percentile of weight for each week of gestation within the Geisinger population from 2006-2013. While creating the *a priori* outcomes, we discovered that maternal and fetal specialists often use the electronic health record problem list to identify a pregnancy as high-risk. Because we hypothesized that UNGD could contribute to conditions (e.g., pulmonary, cardiovascular) that could designate a pregnancy as high-risk, p*ost hoc* we added high-risk pregnancy as an outcome.

Unconventional natural gas development activity index

We collected data, spanning 2005-2013, on well drilling and production dates and volumes from the Pennsylvania Department of Environmental Protection and on well stimulation dates and drilling depth from the Pennsylvania Department of Conservation and Natural Resources. We collaborated with SkyTruth (Shepherdstown, WV, skytruth.org) to use crowdsourcing to confirm well pad locations using U.S. Department of Agriculture aerial photographs. We imputed missing total depths, production volumes, and stimulation dates from available data. The assembled dataset included latitude and longitude of each well; dates of well spudding (i.e., beginning of drilling), perforation, stimulation, and production; total well depth; volume of natural gas produced; and the number of producing days annually. Because phases of unconventional natural gas development (i.e., pad development, drilling, stimulation, production) are known to differ by exposures and duration, we derived individual-level estimates to each of these four phases. Although there was heterogeneity by well, for the purposes of exposure assignment, we used published descriptions[34] of the process and information in our own data to estimate phase durations: (1) pad development = the 30 days prior to the first well drilled on a pad; (2) drilling = 1-30 days, based on total well depth; (3) hydraulic fracturing = 7 days; and (4) production = present when reported production values were non-zero.

We first created four exposure metrics by phase that incorporated all wells statewide as:

$$Mother \quad j \quad metric = \sum_{i=1}^{n} \sum_{k=1}^{l} m\left(I_A\left(k\right)\right) / {d_{ij}}^2$$

where *n* was the number pads or wells; *k* was the day with 1 equal to January 1, 2009 and *l* was equal to 1125 or January 31, 2013; *m* was 1 for pad and drilling, *m* was total well depth for stimulation (because we used total well depth as a surrogate for truck trips and hydraulic

fracturing fluid volume), and *m* was gas volume for production (because we used production volume as a surrogate for air pollution emissions); $I_A(k)$ was 1 when the phase overlapped temporally with gestation; and d_{ij}^2 was the squared-distance between the coordinates of pad or well *i* and mother *j*'s home address. The phase-specific units were pads/m^2, wells/m^2, total well depth (m)/m^2, and gas production volume m^3/m^2 for pad, drilling, stimulation, and production metrics, respectively. The denominator was always the squared-distance between wells and residences (m^2).

Because we wanted to estimate exposure to phases of unconventional natural gas development and there was collinearity between the four exposure metrics (ρ, 0.6-0.9), each was z-transformed then summed to estimate the unconventional natural gas development activity index (hereafter referred to as the activity index). This meant that a woman living close to several well pads under development, but far from any producing wells could have a similar index as a woman living near only producing wells. We did not evaluate trimester-specific indices because of very high inter-trimester correlations. We divided the aggregated activity index into quartiles for analysis.

Covariates

We included clinical, demographic, and environmental covariates to control for potential confounding based on *a priori* hypotheses and previous studies of birth outcome risk factors including neonate sex, gestational age (for birth weight), season and year of birth, maternal age, race/ethnicity, Geisinger primary care provider status, smoking status during pregnancy, pre-pregnancy body-mass index (BMI), parity, antibiotic orders during pregnancy, and receipt of Medical Assistance, a surrogate for low family socioeconomic status.[35,36] For teenagers (≤20 years), we categorized pre-pregnancy BMI using z-scores based on U.S. Centers for Disease Control and Prevention data. Environmental covariates included distance to nearest major road (principal arterial and larger based on U.S. Census Bureau Topologically Integrated Geographic Encoding and Referencing road files),[24,37] community socioeconomic deprivation[38] and residential greenness (based on the average normalized difference vegetation index values in the 1250m × 1250m area surrounding the residence in the three seasons prior to delivery).[39] Due to concern about the potential contamination of ground water in the region, we used Pennsylvania Department of Environmental Protection public water service areas to assign household water source as municipal or well water.[12,40] Alcohol use was not a confounder, so was not included in adjusted models. We also did not adjust for blood pressure or the number of prenatal healthcare visits because we considered them potential mediators.

Statistical analysis

To assess the association of the activity index (quartiles) with birth outcomes, we fit a series of multilevel linear (for birth weight) and logistic (for other outcomes) regression models with random intercepts for mother and community to account for nesting of observations in women and place. The mother-specific intercept incorporated prior pregnancy outcomes (e.g., prior preterm birth) into our models. We selected final models by a combination of *a priori* hypotheses and likelihood ratio tests (P-value < 0.10). For each outcome, model 1 was adjusted for sex of the neonate and season of birth, maternal age at delivery (linear and

quadratic, years), maternal race/ethnicity (white, black, Hispanic, other), primary care status (yes vs. no), smoking status during pregnancy (never, former, current, or conflicting/missing), pre-pregnancy BMI (underweight: z-score > 2SD below mean or < 18.5 kg/m^2; normal: z-score within 1 SD of mean or 18.5-24.9 kg/m^2; overweight: z-score 1-2 SD above mean or 25-29.9 kg/m^2; or obese: z-score > 2 SD above mean or ≥ 30 kg/m^2), parity (nulliparous vs. multiparous), receipt of Medical Assistance (never vs. ever), delivery hospital (Geisinger Medical Center vs. Geisinger Wyoming Valley), distance to nearest major road in meters, drinking water source (well water vs. municipal), community socioeconomic deprivation (quartiles), and greenness (continuous). In model 2, we further adjusted associations for year (2009-2010 vs. 2011-2013). Birth weight models were also adjusted for gestational age (linear and quadratic, weeks) and high-risk pregnancy models were additionally adjusted for the average annual number of entries on the problem list to account for the fact that its use increased over time (mean of 14% more entries per year).

In sensitivity analyses we included the number of antibiotic orders during pregnancy, restricted preterm models to neonates born moderately to late preterm (32-36 weeks gestation), and fit a Cox proportional hazard model with gestational age as the timescale, preterm birth as the outcome, unconventional natural gas development varying by week, and robust standard errors. We also assessed the possibility of unobserved confounding by assigning babies born in 2006, before there was any unconventional natural gas development, the estimated exposure metric they would have accrued had they been born in 2012, when there was such development. If the 2012 unconventional natural gas development exposure metric were found to be associated with birth outcomes for these 2006 babies, it would suggest that our main study findings may have been spurious.

We report associations as difference in term birth weight or odds ratios for preterm birth, small for gestational age, 5-minute Apgar score, and high-risk pregnancy comparing ≥ quartile 2 of unconventional natural gas development activity to quartile 1 with 95% confidence intervals. Models did not exhibit residual spatial variation, which we checked for by visually inspecting semivariograms.[41] Because of the low proportion of missing data (0-1.4% on outcomes and 0-5.2% on confounders) and because missingness only appeared to be associated with year (more missing data in earlier years), patients were omitted from models when they were missing data. We used Stata version 13 (StataCorp. College Station, TX) and R version 3.0.0 (R Foundation for Statistical Computing).

RESULTS

We identified 20598 neonates born to 20569 mothers who delivered between 2006 and January 2013. After exclusions (Figure 1), we reached a final study sample of 9384 mothers who delivered 10496 neonates (mean of 1.2 per mother). Mothers lived in 699 communities (mean of 14 per community). In eTable 1 we compare the final population to those excluded. Geisinger patients had residential stability. We compared addresses from 2010 and 2013 on 333,222 patients and found that 79.8% had the exact same street address, 6.0% had moved <1500m and another 10% had moved 1500-16,000m from their original address.

The mean birth weight was 3272 grams (SD = 612). Eleven percent (n = 1103) of the births were preterm, 8% were moderately preterm (n = 871), 2% (n = 227) had 5 minute Apgar scores < 7, 10% (n = 1024) were small for gestational age, as expected given our use of an internal standard, and 27% (n = 2853) of pregnancies were identified as high-risk (Table 1).

Unconventional natural gas development in the Pennsylvania Marcellus shale began in the southwest in 2005 (15 wells drilled) and quickly accelerated. By the period 2009-2012, an average of 1555 unconventional wells, drilled to an average depth of 3380m, and 1177 wells entered production annually (Figure 2). The mean (SD), median (IQR) number of wells within 20 km of mothers (during their pregnancy) in the first vs. fourth quartile of exposure to unconventional natural gas development was 6 (28), 0 (0-1) vs. 124 (202), 8 (1-122), respectively, reflecting a marked difference in intensity of potential exposure.

In Table 1 and 2 we present descriptive statistics of several demographic and clinical variables by UNGD activity quartile and by outcome. Neonates born in later years and in the summer and fall; and mothers that were multiparous, received an antibiotic order during pregnancy, used well water, or lived farther from the nearest major road appeared to have higher exposure to unconventional natural gas development activity. Among those with poor pregnancy outcomes, several covariates were more common including receipt of Medical Assistance, black race/ethnicity, ever-smoking, and others (Table 2). Mothers with a primary care provider had an average of 16 prenatal visits (SD = 6) compared to 12 (SD = 7) in those without.

The activity index was not associated with adverse birth outcomes in unadjusted analyses (Table 1). In adjusted birth weight and preterm models, current smoking, underweight BMI, nulliparity, high community socioeconomic deprivation (preterm only), and black race/ethnicity and receipt of Medical Assistance (birth weight only) were positively associated; normal BMI, never smoking, farther distance to nearest major road, and higher residential greenness (preterm only) were negatively associated.

After adjustment for covariates, the fourth quartile of the activity index was associated with lower term birth weight, but not after further adjustment for year (Table 3). In adjusted models, the odds of preterm birth increased across quartiles of the activity index (fourth vs. first quartile, 1.4 [95% CI: 1.0-1.9]) (Table 3). This association strengthened with adjustment for year (Table 3), persisted in a survival model framework (eTable 2), and was robust to restriction to moderate and late preterm births (fourth vs. first quartile, OR = 1.5 [95% CI = 1.0-2.4]). In model 2, antibiotic orders were associated with preterm birth (OR = 1.5 [95% CI = 1.3-1.6]). Unconventional natural gas development exposure during the prenatal period was associated with high-risk pregnancy (fourth vs. first quartile of the activity index, OR = 1.3 [95% CI: 1.1-1.7]), but not with 5 minute Apgar score or small for gestational age (results not shown).

In a sensitivity analysis in infants born in 2006 (n = 1932), future exposure to unconventional natural gas development was not associated with preterm birth, Apgar score, or small for gestational age birth in fully adjusted models. Neonates born in 2006, who

would have been in the 4th quartile of the activity index had they been born in 2012, had lower birth weights (β = −53 [95% CI −120 to 12]).

DISCUSSION

We used electronic health record data to conduct a population-based retrospective cohort study in central and northeast Pennsylvania during a time of very rapid unconventional natural gas development in the region. Our study examined associations between prenatal exposure to unconventional natural gas development activity and four birth outcomes and high-risk pregnancy in the mother. We demonstrated that mothers with higher activity index values during pregnancy were more likely to give birth preterm, a finding corroborated in time-to-delivery analysis, and to have a physician-recorded high-risk pregnancy. An association with term birth weight was not robust to adjustment for year. In a sensitivity analysis, when we assigned babies born in 2006 the activity index they would have had if they were born in 2012, unconventional natural gas development was associated with lower birth weight, suggesting that the primary association may have been due, at least in part, to unobserved confounding. There were no associations with Apgar score or small for gestational age. The electronic health record allowed us to carefully ascertain both pregnancy outcomes and confounding variables. We were able to control for other community conditions and exposures, including distance to roadways, source of drinking water, and community socioeconomic deprivation. To our knowledge, this is also the first study to base estimates of unconventional natural gas development activity exposure in relation to health risks on four separate phases of well development.

Three recent reviews summarized evidence linking health and unconventional natural gas development and found it lacking.[1-3] Werner et al. identified only four highly relevant peer-reviewed studies related to these processes and health outcomes: two using self-reported symptoms, one of childhood cancer that may not have adequately accounted for latency, and one of birth outcomes.[21,22,26,30] The only published study dealing with birth outcomes reported that density and proximity of gas wells in Colorado, USA, were associated with two birth defects, but also higher birth weight and lower odds of preterm birth.[26] During the study period, the U.S. Energy Information Administration reported that Colorado produced 28 million cubic meters of natural gas unconventionally and 130 million cubic meters conventionally. We were able to study people living in areas with much higher unconventional natural gas development activity; Pennsylvania produced 58 billion cubic meters of natural gas unconventionally in 2012. A second, unpublished study, compared neonates born to mothers residing within 2.5 km of a spudded well to those living within 2.5 km of a permitted, but not spudded, well.[27] This study reported decreased term birth weight (but did not control for gestational age) and increased small for gestational age and 5 minute Apgar scores < 8, but no association with preterm birth. We too observed associations with Apgar scores < 8, but not < 7, as most prior studies have used, and between unconventional natural gas development and term birth weight when we omitted gestational age.

The unconventional natural gas development process is associated with heterogeneous exposures that last varying amounts of time. We did not have the capability to measure exposures directly. However, we were able to account for the varying durations of the

different phases by using published descriptions and information from our own analysis to assign deliveries activity values in defined windows. This should be an improvement over prior studies, which generally used spud date to identify the start of an exposure assumed to last forever, an incorrect assumption.[26,30] Any bias introduced by errors in the estimation of the durations of development phases is likely to be independent of birth outcomes and thus tend to bias associations towards the null.

There are multiple ways unconventional natural gas development activity could influence birth outcomes. Concerns include impacts on air quality,[1-3] ground and surface water quality,[12] and maternal psychosocial stress from noise, increased traffic volumes, and contextual exposures including social disruption and community livability.[4] For many of these, their associations with birth outcomes have been investigated in other settings.[14,17,37,42] For instance, prior literature suggests that a 10μg/m^3 increase in exposure to $PM_{2.5}$ is associated with a 10% increase in odds of preterm birth and low birth weight.[15,18] There are also several proposed mechanisms linking PM exposure to preterm birth including interference with placental development, inflammation, and increased risk of infection.[18] In our study, mothers with higher activity indices were indeed more likely to receive an antibiotic order during their pregnancy. Neighborhood contextual factors have also been consistently associated with birth outcomes.[43] Women living in communities exposed to unconventional natural gas development likely experience both environmental and social exposures that may have synergistic effects on health.[44] Finally, unmeasured confounding could have contributed to our results; our measure of family SES was binary and did not include education, and we also had no information on occupation.

This study had limitations. In an effort to assign activity values more accurately than prior studies, we estimated the duration of each phase of unconventional natural gas development. This is likely to have introduced measurement error since the amount of time each phase lasts varies by well. We used a distance-based metric to estimate exposure to four phases of development, but were not able to evaluate phase-specific associations due to collinearity. Phases are known to contribute different types of exposures (e.g., pad development is a source of diesel emissions including PM as well as noise),[1] but our methodology did not allow us to differentiate among phase-specific exposures, type of hazardous exposure (e.g., air and water pollution), and the contextual effects of development. We were not able to take environmental samples, which may have led to exposure misclassification and prevented us from determining if a specific pollutant was responsible for our associations. Additionally, unconventional natural gas development was highly correlated with year, making it challenging to control for temporal trends; therefore we presented results both unadjusted and adjusted for year. In regards to conventional gas development in the state, although the densest development is in the northwest and many of these wells are decades old and non-producing, there was still collinearity between our activity index and conventional gas proximity metrics, which precluded adjustment for conventional gas well locations. Historical addresses are not retained in the Geisinger electronic health record so we were not able to determine whether the last recorded address represented residential location during the course of pregnancy. Our sensitivity analysis suggested that most Geisinger patients do not move, and if they do, they tend to move locally. In our study, many wells were developed in one location over time, so the exposures, emissions, and community

circumstances present in one trimester were likely present in another. This collinearity prevented us from evaluating trimester-specific associations.

Prior studies found elevated symptoms in regions with unconventional natural gas development and concern by residents of possible health effects. This study adds to limited evidence that unconventional natural gas development adversely affects birth outcomes. We observed that an index of development activity was associated with both preterm birth and high-risk pregnancy. Multiple aspects of development might be involved, including hazardous exposures and contextual effects. Future studies should use direct environmental sampling to more accurately capture exposure and include data on mother's place of residence throughout pregnancy. Such data is needed to allow policy makers to effectively weigh the risks and benefits of unconventional natural gas development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Joseph J. DeWalle, Jennifer K. Irving, Joshua M. Crisp, and Awathif Mackeen at the Geisinger Center for Health Research (Danville, PA, USA) for patient geocoding, assistance in assembling the UNGD dataset, and valuable comments on the manuscript; and Peter James at the Harvard School of Public Health (Boston, Massachusetts) and Chih-Da (John) Wu at the National Chiayi University (Chiayi City, Taiwan) for providing the NDVI data.

Source of Funding:

This study was funded by the National Institute of Environmental Health Sciences grant ES023675-01 (PI: B Schwartz) and training grant ES07141 (S Rasmussen). Additional support was provided by the Degenstein Foundation for compilation of well data, the Robert Wood Johnson Foundation Health & Society Scholars program (J Casey), and the National Science Foundation Integrative Graduate Education and Research Traineeship (S Rasmussen).

REFERENCES

1. Adgate JL, Goldstein BD, McKenzie LM. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol. 2014; 48(15):8307–20. [PubMed: 24564405]
2. Shonkoff SB, Hays J, Finkel ML. Environmental public health dimensions of shale and tight gas development. Environ Health Perspect. 2014; 122(8):787–95. [PubMed: 24736097]
3. Werner AK, Vink S, Watt K, Jagals P. Environmental health impacts of unconventional natural gas development: A review of the current strength of evidence. Sci Total Environ. 2015; 505C:1127–41. [PubMed: 25461113]
4. Witter RZ, McKenzie L, Stinson KE, Scott K, Newman LS, Adgate J. The use of health impact assessment for a community undergoing natural gas development. Am J Public Health. 2013; 103(6):1002–10. [PubMed: 23597363]
5. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ. 2012; 424:79–87. [PubMed: 22444058]
6. Macey GP, Breech R, Chernaik M, et al. Air concentrations of volatile compounds near oil and gas production: a community-based exploratory study. Environ Health. 2014; 13:82. [PubMed: 25355625]

7. Roy AA, Adams PJ, Robinson AL. Air pollutant emissions from the development, production, and processing of Marcellus Shale natural gas. J Air Waste Manag Assoc. 2014; 64(1):19–37. [PubMed: 24620400]
8. Vinciguerra T, Yao S, Dadzie J, et al. Regional air quality impacts of hydraulic fracturing and shale natural gas activity: Evidence from ambient VOC observations. Atmos Environ. 2015; 110(0):144–50.
9. Paulik LB, Donald CE, Smith BW, et al. Impact of Natural Gas Extraction on PAH Levels in Ambient Air. Environ Sci Technol. 2015; 49(8):5203–10. [PubMed: 25810398]
10. Kassotis CD, Tillitt DE, Davis JW, Hormann AM, Nagel SC. Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. Endocrinology. 2014; 155(3):897–907. [PubMed: 24424034]
11. Jackson RB, Vengosh A, Darrah TH, et al. Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. Proc Natl Acad Sci U S A. 2013; 110(28):11250–5. [PubMed: 23798404]
12. Llewellyn GT, Dorman F, Westland JL, et al. Evaluating a groundwater supply contamination incident attributed to Marcellus Shale gas development. Proc Natl Acad Sci U S A. 2015
13. Graham J, Irving J, Tang X, et al. Increased traffic accident rates associated with shale gas drilling in Pennsylvania. Accident Anal Prev. 2015; 74(0):203–9.
14. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ Res. 2012; 117:100–11. [PubMed: 22726801]
15. Dadvand P, Parker J, Bell ML, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect. 2013; 121(3):267–373. [PubMed: 23384584]
16. Pedersen M, Giorgis-Allemand L, Bernard C, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir Med. 2013; 1(9):695–704. [PubMed: 24429273]
17. Dadvand P, Basagana X, Figueras F, et al. Air pollution and preterm premature rupture of membranes: a spatiotemporal analysis. Am J Epidemiol. 2014; 179(2):200–7. [PubMed: 24125920]
18. Pereira G, Belanger K, Ebisu K, Bell ML. Fine particulate matter and risk of preterm birth in Connecticut in 2000-2006: a longitudinal study. Am J Epidemiol. 2014; 179(1):67–74. [PubMed: 24068199]
19. Saberi P, Propert KJ, Powers M, Emmett E, Green-McKenzie J. Field survey of health perception and complaints of Pennsylvania residents in the Marcellus Shale region. Int J Environ Res Public Health. 2014; 11(6):6517–27. [PubMed: 25003172]
20. Rabinowitz PM, Slizovskiy IB, Lamers V, et al. Proximity to natural gas wells and reported health status: results of a household survey in Washington County, Pennsylvania. Environ Health Perspect. 2015; 123(1):21–6. [PubMed: 25204871]
21. Perry SL. Using ethnography to monitor the community health implications of onshore unconventional oil and gas developments: examples from Pennsylvania's Marcellus Shale. New Solut. 2013; 23(1):33–53. [PubMed: 23552647]
22. Steinzor N, Subra W, Sumi L. Investigating links between shale gas development and health impacts through a community survey project in Pennsylvania. New Solut. 2013; 23(1):55–83. [PubMed: 23552648]
23. Casey JA, Ogburn EL, Rasmussen SG, et al. Predictors of Indoor Radon Concentrations in Pennsylvania, 1989-2013. Environ Health Perspect. 2015
24. Dadvand P, Ostro B, Figueras F, et al. Residential proximity to major roads and term low birth weight: the roles of air pollution, heat, noise, and road-adjacent trees. Epidemiology. 2014; 25(4): 518–25. [PubMed: 24787556]
25. Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. Women and Birth. 2015
26. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect. 2014; 122(4):412–7. [PubMed: 24474681]

27. Hill, EL. Shale Gas Development and Infant Health: Evidence from Pennsylvania. 2013. http://dyson.cornell.edu/research/researchpdf/wp/2012/Cornell-Dyson-wp1212.pdf (accessed 5/15/2015)
28. Kovats S, Depledge M, Haines A, et al. The health implications of fracking. Lancet. 2014; 383(9919):757–8. [PubMed: 24581655]
29. Mitka M. Rigorous evidence slim for determining health risks from natural gas fracking. JAMA. 2012; 307(20):2135–6. [PubMed: 22618904]
30. Fryzek J, Pastula S, Jiang X, Garabrant DH. Childhood cancer incidence in Pennsylvania counties in relation to living in counties with hydraulic fracturing sites. J Occup Environ Med. 2013; 55(7): 796–801. [PubMed: 23836020]
31. Schwartz BS, Stewart WF, Godby S, et al. Body mass index and the built and social environments in children and adolescents using electronic health records. Am J Prev Med. 2011; 41(4):e17–e28. [PubMed: 21961475]
32. Casey, JA. Spatial and molecular characterization of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in relation to high-density livestock production in Pennsylvania. Johns Hopkins Bloomberg School of Public Health; Baltimore, MD: 2014. PhD Dissertation
33. Stuart A, Olausson PO, Källen K. Apgar scores at 5 minutes after birth in relation to school performance at 16 years of age. Obstet Gynecol. 2011; 118(2):201–8. Part 1. [PubMed: 21734618]
34. New York State Department of Environmental Conservation. Final Supplemental Generic Environmental Impact Statemet on Oil, Gas, and Solution Mining Regulatory Program. 2015. http://www.dec.ny.gov/docs/materials_minerals_pdf/fsgeis2015.pdf (accessed 5/15/15)
35. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606):75–84. [PubMed: 18177778]
36. Valero De Bernabe J, Soriano T, Albaladejo R, et al. Risk factors for low birth weight: a review. Eur J Obstet Gynecol Reprod Biol. 2004; 116(1):3–15. [PubMed: 15294360]
37. Padula AM, Mortimer K, Hubbard A, Lurmann F, Jerrett M, Tager IB. Exposure to traffic-related air pollution during pregnancy and term low birth weight: estimation of causal associations in a semiparametric model. Am J Epidemiol. 2012; 176(9):815–24. [PubMed: 23045474]
38. Vos AA, Posthumus AG, Bonsel GJ, Steegers EA, Denktas S. Deprived neighborhoods and adverse perinatal outcome: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2014; 93(8):727–40. [PubMed: 24834960]
39. Hystad P, Davies HW, Frank L, et al. Residential greenness and birth outcomes: evaluating the influence of spatially correlated built-environment factors. Environ Health Perspect. 2014; 122(10):1095–102. [PubMed: 25014041]
40. Manassaram DM, Backer LC, Moll DM. A review of nitrates in drinking water: maternal exposure and adverse reproductive and developmental outcomes. Ciencia & saude coletiva. 2007; 12(1): 153–63. [PubMed: 17680066]
41. Cressie, N. Statistics for Spatial Data. J. Wiley & Sons, Inc; 1991.
42. Gehring U, Tamburic L, Sbihi H, Davies HW, Brauer M. Impact of noise and air pollution on pregnancy outcomes. Epidemiology. 2014; 25(3):351–8. [PubMed: 24595395]
43. Metcalfe A, Lail P, Ghali WA, Sauve RS. The association between neighbourhoods and adverse birth outcomes: a systematic review and meta-analysis of multi-level studies. Paediatr Perinat Epidemiol. 2011; 25(3):236–45. [PubMed: 21470263]
44. Erickson AC, Arbour L. The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development. J Environ Public Health. 2014; 2014:901017. [PubMed: 25574176]

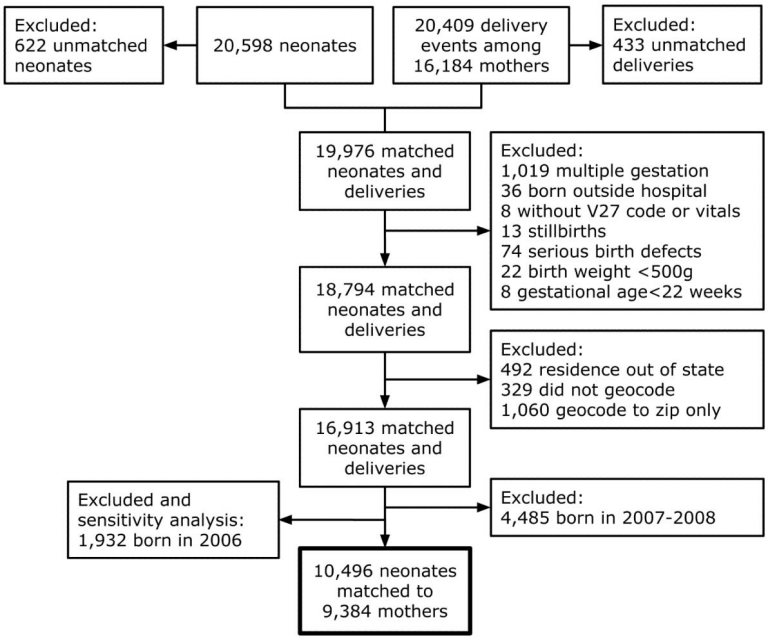


Figure 1.
Flow diagram of study population assembly

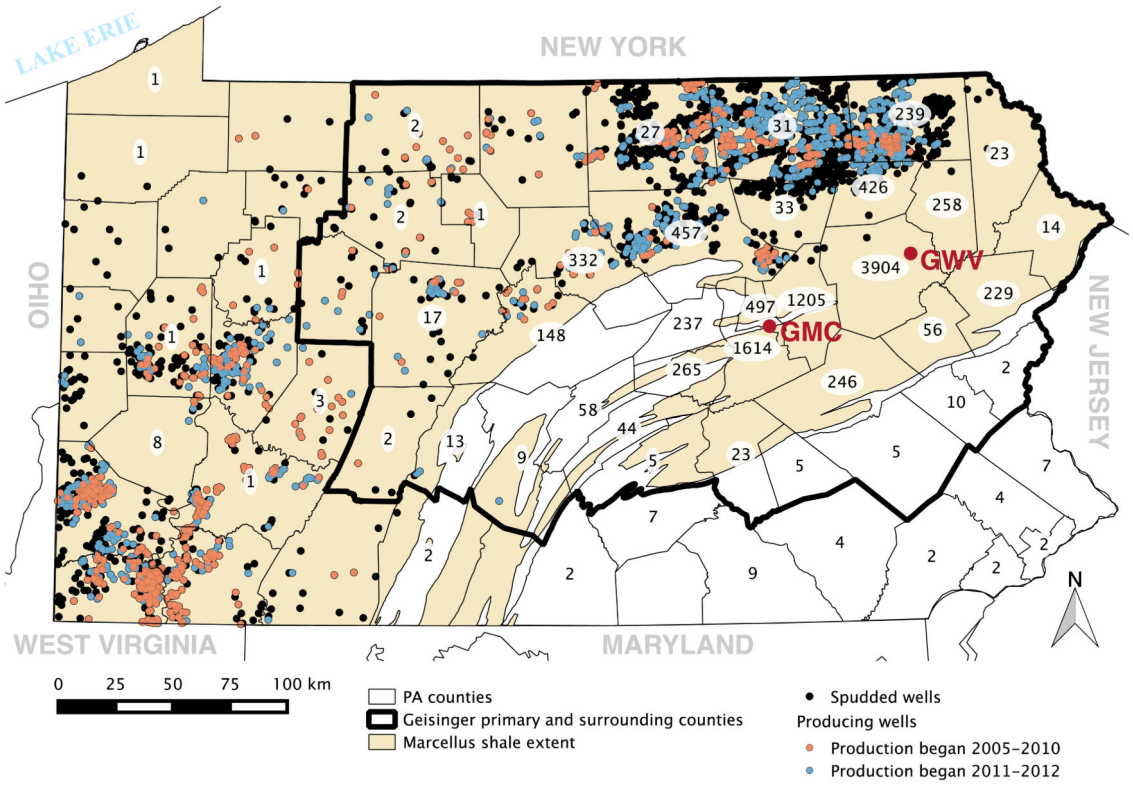


Figure 2.

The Marcellus shale extent, the location of spudded and producing wells as of December 2012, the location of the two Geisinger Health System hospitals and the primary and surrounding Geisinger counties. Annotation indicates the number of neonates born to mothers residing in each county. GMC = Geisinger Medical Center. GWV = Geisinger Wyoming Valley.

Table 1

Distribution of study population characteristics among 9384 mothers and their 10496 children by quartile of unconventional natural gas development (UNGD) activity index

		UNGD activity index quartile[a]			
Variable	**No. (%)**	**1**	**2**	**3**	**4**
Maternal characteristics					
Age at birth, years, mean (SD)	10496 (100)	27.6 (5.8)	27.8 (5.7)	27.9 (5.7)	27.8 (5.8)
Race/ethnicity, %					
White	9327 (89)	88	89	86	92
Black	382 (4)	4	3	4	3
Hispanic	601 (6)	6	6	7	3
Other	148 (1)	2	1	2	1
Missing	38 (<1)	<1	<1	<1	<1
Primary care patient, %	4789 (46)	45	45	46	46
Smoking status[b], %					
Never	4984 (47)	46	45	49	49
Former	2258 (22)	21	24	21	20
Current	1785 (17)	18	18	15	17
Conflicting or missing	1489 (14)	15	13	15	14
Alcohol use during pregnancy[b], %					
No	8448 (80)	77	79	83	83
Yes	1412 (13)	14	14	13	13
Missing	636 (6)	9	7	4	4
Pre-pregnancy body-mass index (kg/m^2), %					
<18.5	222 (2)	2	2	2	2
18.5-24.9	3878 (37)	37	38	36	36
25-29.9	2834 (27)	27	25	28	28
≥30	3013 (29)	29	30	28	28
Missing	549 (5)	5	5	5	5
Pre-pregnancy blood pressure, %					
Systolic >140mmHg or diastolic >90mmHg	1125 (11)	9	11	13	10
Normal	9371 (89)	91	89	87	90
Nulliparous, %	4600 (44)	47	43	44	41
Healthcare visits during pregnancy, n, mean (SD)	10496 (100)	14.4 (6.3)	13.8 (6.4)	13.6 (6.7)	13.7 (6.7)
Antibiotic order during pregnancy, %	3338 (32)	30	31	31	35
Receipt of Medical Assistance, %	4796 (46)	44	47	45	47
Delivery hospital, %					
Geisinger Medical Center	5638 (54)	57	57	51	49

		UNGD activity index quartile[a]			
Variable	**No. (%)**	**1**	**2**	**3**	**4**
Geisinger Wyoming Valley	4858 (46)	43	43	49	51
Distance to nearest major road, m, median (IQR)	10496 (100)	788 (284-2825)	863 (304-3229)	609 (237-1826)	1373 (455-6757)
Drinking water source, %					
Municipal water	7306 (70)	72	72	78	57
Well water	3190 (30)	28	28	22	43
Community socioeconomic deprivation[c], %					
Quartile 1	2590 (25)	25	23	24	27
Quartile 2	2648 (25)	23	22	23	28
Quartile 3	2642 (25)	25	23	24	29
Quartile 4	2616 (25)	27	33	29	15
Residential greenness, NDVI index, mean (SD)	0.54 (0.10)	0.50 (0.11)	0.56 (0.09)	0.54 (0.09)	0.54 (0.11)
Infant Characteristics					
Male, %	5372 (51)	51	52	52	50
Birth weight, grams, mean (SD)	10495 (100)	3289 (604)	3249 (623)	3286 (599)	3264 (622)
Gestational age, weeks, mean (SD)	10418 (99)	38.9 (2.2)	38.9 (2.4)	39.0 (2.1)	38.9 (2.3)
Preterm birth <37 weeks, %	1103 (11)	10	11	10	11
Preterm birth 32 to 36 weeks, %	871 (8)	2	2	2	2
Small for gestational age, %	1024 (10)	9	10	10	10
Apgar score, %					
5 minute, <7	227 (2)	2	2	2	2
5 minute, ≥7	10199 (95)	97	97	97	97
5 minute, missing	70 (<1)	1	<1	1	1
High-risk pregnancy[d], %	2853 (27)	17	25	33	33
Birth year, %					
2009	2336 (22)	79	7	1	2
2010	2518 (24)	20	55	9	11
2011	2608 (25)	1	27	49	22
2012	2852 (27)	<1	11	38	60
2013	182 (2)	0	<1	2	5
Birth season, %					
December-February	2562 (24)	27	20	25	24
March-May	2605 (25)	29	25	24	21
June-August	2748 (26)	23	29	25	27
September-November	2581 (25)	20	26	25	27

UNGD activity index quartile was assigned based on 4 z-transformed indicators using inverse-distance squared models that incorporated distance to the mother's home; dates and durations of the phases (well pad development, spudding, hydraulic fracturing, and production); and well characteristics (depth and production volume) during gestation, and is in standard deviation units. Percentages are rounded to whole numbers.

EHR = electronic health record. IQR = interquartile range. NDVI = normalized difference vegetation index.

[a] Quartile 1: <−0.44; Quartile 2: −0.43 to −0.15, Quartile 3: −0.14 to 0.18, Quartile 4: >0.18.

[b] Smoking, alcohol use, and high-risk pregnancy were reported during pregnancy in the EHR social history and problem list.

[c] Community socioeconomic deprivation was assigned at the township, borough, or census tract level, based on 6 indicators derived from the U.S. Census American Community Survey 2012 5-year estimates: combined less than high school education, not in the labor force, in poverty, on public assistance, civilian unemployment, and does not own a car; a higher score represents a more deprived community.

[d] Defined based on physician-reported high-risk pregnancy.

Table 2

Distribution of outcomes by selected covariates

	Outcome				
	Birth weight, g, median (IQR)	**Preterm birth, n (%)**	**5 min Apgar <7, n (%)**	**SGA, n (%)**	**High risk pregnancy[a], n (%)**
N	10495	1103	10426	1024	2853
Pre-pregnancy body-mass index (kg/m^3)					
<18.5	3051 (2696-3359)	50 (23)	7 (3)	41 (19)	66 (30)
18.5-24.9	3258 (2903-3575)	408 (11)	80 (2)	443 (12)	1008 (26)
25-29.9	3352 (2991-3685)	265 (9)	66 (2)	267 (10)	751 (26)
≥30	3404 (3071-3745)	286 (10)	57 (2)	222 (7)	940 (31)
Missing	3263 (2908-3631)	94 (17)	17 (3)	51 (10)	89 (16)
Parity					
Nulliparous	3303 (2940-3625)	486 (11)	116 (2)	525 (12)	981 (21)
Multiparous	3338 (2991-3686)	617 (10)	111 (2)	499 (9)	1872 (32)
Antibiotic order during pregnancy					
No	3348 (3012-3679)	580 (8)	131 (2)	686 (10)	1891 (26)
Yes	3268 (2885-3617)	523 (16)	96 (3)	338 (10)	962 (29)
Year of birth					
2009 and 2010	3330 (2974-3665)	528 (11)	90 (2)	455 (10)	888 (18)
2011, 2012, and 2013	3314 (2968-3657)	575 (10)	138 (2)	569 (10)	1965 (35)
Delivery hospital					
Geisinger Medical Center	3284 (2884-3630)	874 (16)	180 (3)	554 (10)	1507 (27)
Geisinger Wyoming Valley	3365 (3050-3688)	229 (5)	47 (1)	470 (10)	1346 (28)
Community socioeconomic deprivation[b]					
Quartile 1	3372 (3033-3700)	249 (10)	67 (3)	205 (8)	597 (23)
Quartile 2	3345 (2984-3667)	264 (10)	49 (2)	241 (9)	705 (27)
Quartile 3	3303 (2944-3640)	306 (12)	53 (2)	262 (10)	727 (28)
Quartile 4	3264 (2925-3620)	284 (11)	58 (2)	316 (12)	824 (32)

Percentages are rounded to whole numbers.

EHR = electronic health record. IQR = interquartile range. SGA = small for gestational age.

[a] Reported in EHR problem list during pregnancy.

[b] Community socioeconomic deprivation was assigned at the township, borough, or census tract level, based on 6 indicators derived from the US Census American Community Survey 2012 5-year estimates: combined less than high school education, not in the labor force, in poverty, on public assistance, civilian unemployment, and does not own a car; a higher score represents a more deprived community.

Table 3

Associations of term birth weight and preterm birth and exposure to unconventional natural gas development (UNGD) activity

	Model 1A[a]	Model 2A[b]	Model 1B[c]	Model 2B[d]
	Term birth weight (g)		Preterm birth	
Variable	**Difference (95% CI)**	**Difference (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
UNGD activity quartile	N = 8839	N = 8839	N = 9848	N = 9848
1	Reference	Reference	1.0	1.0
2	−21 (−46 to 5)	−16 (−44 to 11)	1.2 (0.9-1.6)	1.3 (1.0-1.8)
3	−9 (−35 to 16)	1 (−34 to 36)	1.3 (1.0-1.7)	1.6 (1.1-2.4)
4	−31 (−57 to -5)	−20 (−56 to 16)	1.4 (1.0-1.9)	1.9 (1.2-2.9)
Year of birth				
2009 or 2010		Reference		1.0
2011, 2012, or 2013		12 (−15 to 39)		1.3 (1.0-1.8)

CI=confidence interval. OR = odds ratio.

[a] Model 1A was adjusted for sex and gestational age of neonate; maternal characteristics: age at delivery, race/ethnicity, primary care patient status, smoking status, pre-pregnancy body mass index, parity, number of antibiotic orders during pregnancy, receipt of Medical Assistance, delivery hospital, drinking water source, distance to nearest major road, mean residential greenness during pregnancy; and community socioeconomic deprivation quartile.

[b] Model 2A further adjusted for year of birth.

[c] Model 1B was adjusted for sex of neonate; maternal characteristics: age at delivery, race/ethnicity, primary care patient status, smoking status, pre-pregnancy body mass index, parity, receipt of Medical Assistance, delivery hospital, drinking water source, distance to nearest major road, mean residential greenness during pregnancy; and community socioeconomic deprivation quartile.

[d] Model 2B further adjusted for year of birth.

Published in final edited form as:
Epidemiology. 2014 January ; 25(1): 44–47. doi:10.1097/EDE.0000000000000030.

Interaction of the MET Receptor Tyrosine Kinase Gene and Air Pollution Exposure in Autism Spectrum Disorder

Heather E. Volk[1,2,3], **Tara Kerin**[1], **Fred Lurmann**[4], **Irva Hertz-Picciotto**[5], **Rob McConnell**[1], and **Daniel B. Campbell**[3,6,7]

[1]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

[2]Department of Pediatrics, Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA

[3]Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA

[4]Sonoma Technology, Inc

[5]Department of Public Health Sciences, University of California, Davis, Davis, CA

[6]Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA

[7]Center for Genomic Psychiatry, Keck School of Medicine, University of Southern California, Los Angeles, CA

Abstract

Background—Independent studies report association of autism spectrum disorder with air pollution exposure and a functional promoter variant (rs1858830) in the MET receptor tyrosine kinase (*MET*) gene. Toxicologic data find altered brain Met expression in mice after prenatal exposure to a model air pollutant. Our objective was to investigate whether air pollution exposure and *MET* rs1858830 genotype interact to alter ASD risk.

Methods—We studied 252 cases of autism spectrum disorder and 156 typically developing controls the Childhood Autism Risk from Genetics and the Environment Study. Air pollution exposure was assigned for local traffic-related sources and regional sources (particulate matter, nitrogen dioxide and ozone). *MET* genotype was determined by direct re-sequencing.

Results—Subjects with both *MET* rs1858830 CC genotype and high air pollutant exposures were at increased risk of autism spectrum disorder compared with subjects who had both the CG/GG

Corresponding Author: Heather E. Volk, University of Southern California, 2001 N. Soto Street, MC 9237, Los Angeles, CA 90089 (hvolk@usc.edu); Phone: 323-442-5101; Fax: 323-442-3272.

Financial Disclosures:
Fred Lurmann is employed by Sonoma Technology Inc., Petaluma, CA. Rob McConnell has received support from an air quality violations settlement agreement between the South Coast Air Quality Management District, a California state regulatory agency, and BP. Heather Volk received travel funds from Autism Speaks to present a paper at an academic conference. The other authors declare no competing financial interests.

genotypes and lower pollutant exposures. A statistical test of multiplicative interaction identified a statistically significant effect between NO_2 and *MET* CC genotype (p=0.03)

Conclusions—*MET* rs1858830 CC genotype and air pollutant exposure may interact to increase autism spectrum disorder risk.

Autism and autism spectrum disorders are complex neurodevelopmental disorders characterized by deficits in social interaction, communication, and behavioral flexibility. The complex phenotypic presentation of these disorders suggests that multiple genetic and environmental factors contribute to risk, and gene-environment interactions are widely believed to underlie autism spectrum disorders. Few studies have addressed joint risk from specific genetic susceptibility in combination with a specific environmental exposure or class of exposures.[1] In previous independent studies, we have identified (1) increased autism spectrum disorder risk among children exposed to high levels of local near-roadway traffic-related air pollution and regional particulate matter near the time of birth[2,3]; (2) increased autism spectrum disorder risk among children with the C allele of the *MET* gene promoter variant rs1858830,[4,5] which is associated with decreased expression of MET protein in brain[6] and immune system[7]; and (3) decreased MET protein expression in brain and altered behavior in offspring of mouse dams exposed during pregnancy to the polycyclic aromatic hydrocarbon benzo(a)pyrene (a component of traffic-related air pollution and particulate matter).[8] Based on these independent autism spectrum disorder associations and the biological link between benzo(a)pyrene and *MET*, we hypothesized that a gene-environment interaction contributes to autism spectrum disorder risk.

In children, as in animals, prenatal polycyclic aromatic hydrocarbon exposure has been associated with intelligence (IQ) deficits at age 5 years as well as with increased anxiety, depression, and inattention at age 6–7.[8–10] In this study we investigated the relationship of air pollution exposure and genotype at the *MET* rs1858830 locus with autism spectrum disorder.

Methods

Description of Sample

The Childhood Autism Risks From Genetics and the Environment Study is a population-based, case-control study of preschool children from California. Participants were born in California and lived with at least one English- or Spanish-speaking biologic parent in one of the study catchment areas related to specific regional centers in California. Subjects were 24 to 60 months of age at the time of recruitment; additional details on study design are provided elsewhere.[11] For this analysis, cases met criteria for autism or autism spectrum disorder based on the Autism Diagnostic Observation Schedules and the Autism Diagnostic Interview-Revised. Typically developing controls were children who received a score of less than 15 on the Social Communication Questionnaire and also showed no evidence of other types of developmental delay (composite scores greater than 70 on Mullen Scales of Early Learning and Vineland Adaptive Behavior Scales). We assigned air pollution exposure to 669 study participants based on their residential histories and available exposure databases (as described below).[3] For 63 percent of participants, parents agreed to give blood and

consented to share biospecimens with researchers outside of the original study team. This analysis includes 251 cases with a confirmed diagnosis of autism or autism spectrum disorder and 156 controls with typical development.

In parental interviews we collected data on demographic characteristics, medical conditions and environmental exposures, including residential history.[11] Residential histories recorded dates and address locations where the mother lived, beginning at conception through the most recent place of residence, as well as any other place of residence where the child lived. These dates and addresses were used to develop air pollution exposure metrics.[3] Prenatal and birth addresses were used to develop a weighted average of pollution exposure. In this analysis, we focus on air pollution exposure during the prenatal period.

Air Pollution Exposure Assignment

We assigned modeled estimates of traffic-related air pollution exposure to study participants using the CALINE4 line-source air-quality dispersion model.[12] Included in the model is information on roadway geometry, link-based traffic volumes, period-specific meteorological conditions (wind speed and direction, atmospheric stability, and mixing heights), and vehicle emission rates.[3] CALINE4 pollutant concentration estimates are indicators of the traffic-related air pollutant mixture rather than of a specific pollutant. We estimated residential exposure derived from freeways, non-freeways, and all roads located within 5 km of the home.

We also used regional air quality data to assign exposure for particulate matter less than 2.5 and less than 10 microns in diameter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide, and ozone using data from the US Environmental Protection Agency Air Quality System (www.epa.gov/ttn/airs/airsaqs) supplemented for Southern California by the University of Southern California's Children's Health Study data for 1997–2009.[3] When no Federal Reference/Equivalent Method data for particulate matter were available for a given monitoring station in the Air Quality System, Children's Health Study continuous particulate matter data were used. The monthly air quality data from monitoring stations located within 50 km of each residence were used for spatial interpolation of ambient concentrations. The spatial interpolations were based on inverse distance-squared weighting of data from up to four closest stations located within 50 km of each participant residence; however, if one or more stations were located within 5 km of a residence, then only data from the stations within 5 km were used for the interpolation.

Genotyping Methods

Blood was collected from participants as part of the study protocol, with genomic DNA extracted from peripheral blood leukocytes using standard methods (Puregene kit; Gentra Inc). As the rs1858830 SNP falls within a highly GC-rich region, indirect genotyping methods fail when using genomic DNA. A 652-bp fragment containing the rs1858830 SNP was amplified from 15 ng genomic DNA with primers 5′-GATTTCCCTCTGGGTGGTG-3′ (Forward) and 5′-CAAGCCCCATTCTAGTTTCG-3′ (Reverse). Polymerase chain reaction (PCR) analysis was performed with the KOD Xtreme Hot Start Polymerase kit (EMD Millipore), which is designed to amplify regions with high

GC content. Cycling conditions were: 95°C for 5 min followed by 35 cycles of 95°C for 30s, 68°C for 30s and 72 °C for 1 min. Specific amplification of the 652-bp product was confirmed by agarose gel electrophoresis. Each PCR product was subjected to direct re-sequencing using an ABI 3730xl using Big Dye Terminator chemistry. Genotype at the *MET* rs1858830 locus was determined from the sequencing result using Sequencher software (Gene Codes, Ann Arbor, MI, USA).

Statistical Analysis

Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for air pollution exposure and *MET* genotype. We examined each pollutant separately, categorizing children as "high exposure" if the pregnancy average exposure for traffic related air pollution, $PM_{2.5}$ or PM_{10}, nitrogen dioxide, or ozone was in the top 25% of the exposure distribution. Participants in the other 75% served as "low exposure" in our analyses. These categorizations are consistent with findings identified in our previous work.[3] We also explored more and less extreme exposure-cut points (eTable 1). Because previous research demonstrated an increased risk of autism spectrum disorder due to over-transmission of the C allele and because functional studies suggest the *MET* CC genotype is associated with decreased *MET* expression, we compared the CC genotype to the CG and GG genotypes in our analyses.[5] Analyses were adjusted for potential confounders, including child's sex and ethnicity, maximum education level in the home, maternal age, home ownership and prenatal smoking.

Results

Genotyped subjects were similar to ungenotyped subjects in autism spectrum disorder status and air pollution exposure (eTable 1). Genotyped subjects were less likely to have a mother who smoked during pregnancy and less likely to have high nitrogen dioxide exposure compared with ungenotyped subjects. *MET* rs1858830 genotype frequencies did not vary across cases and controls (χ^2=1.40, 2df). We did not find an increased risk of autism spectrum disorder for the *MET* CC genotype compared with CG/GG genotypes (crude OR= 0.9 [95%CI= 0.6–1.4]). Autism spectrum disorder was associated with exposure to the top quartile of traffic-related air pollution (1.7 [1.0–2.7]), particulate matter less than 10 microns in diameter (2.5 [1.6–4.3]), particulate matter less than 2.5 microns in diameter (1.9 [1.2–3.1]), and nitrogen dioxide (1.7 [1.1–2.7]).

We then parameterized our model based on both *MET* genotype and air pollution exposure. Synergistic effects were observed between *MET* CC genotype and local traffic-related air pollution, regional PM_{10}, and regional nitrogen dioxide exposure; adjusted ORs were, respectively, 2.9 (1.0–10.6), 3.2 (1.3–9.1), and 3.6 (1.3–13), comparing the high-risk genotype and highly exposed children to those with low exposure and without the risk genotype (Table). Statistical tests of multiplicative interaction identified a statistically significant effect between NO_2 and *MET* CC genotype (p=0.03) and borderline significant effects between local traffic-related air pollution and *MET* CC genotype (p=0.09). Analyses exploring alternative cut-points found the persistence of joint effects of traffic-related air pollution and *MET* CC genotype using either lower or higher cut points for defining high

exposure (eTable 2). Joint effects of *MET* CC genotype with PM_{10} or nitrogen dioxide are additionally present at higher cutpoints.

Discussion

Examination of joint pollution and gene effects suggest that subjects with both the *MET* rs1858830 CC genotype and high air pollutant exposure were at increased risk of autism spectrum disorder compared with subjects who had both the CG/GG genotypes and lower air pollutant exposure. Given that the *MET* CC genotype had no impact in the 75% of the population with lower air pollutant exposures, these data suggest a gene-environment interaction for autism spectrum disorder based on *MET* genotype and air pollution exposure. These results require independent replication and a more detailed understanding of the underlying biology. However, these data add to the literature supporting a role for gene-environment interactions in autism spectrum disorder etiology. They also point to the contribution of common alleles for which gene-only analyses show inconsistent evidence of a link to autism spectrum disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support:

NIEHS; ES019002, ES013578, ES007048, ES11269, ES015359, ES016535, and ES011627; EPA Star-R; 823392, 833292; MIND Institute matching funds and pilot grant program.

We thank CHARGE families for participating in this research and CHARGE study staff for their time and effort.

References

1. Schmidt R, Hansen R, Hartiala J, Allayee H, Schmidt L, Tancredi D, Flora Tassone F, Hertz-Picciotto I. Prenatal Vitamins, One-carbon Metabolism Gene Variants, and Risk for Autism. Epidemiology. 2011; 22:476–485. [PubMed: 21610500]
2. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential Proximity to Freeways and Autism in the CHARGE Study. Environ Health Perspect. Jun; 2011 119(6):873–877. [PubMed: 21156395]
3. Volk H, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic Related Air Pollution, Particulate Matter, and Autism Risk. JAMA Psychiatry. 2012; 70(1):71–77. [PubMed: 23404082]
4. Campbell DB, Li C, Sutcliffe JS, Persico AM, Levitt P. Genetic evidence implicating multiple genes in the MET receptor tyrosine kinase pathway in autism spectrum disorder. Autism Res. Jun; 2008 1(3):159–168. [PubMed: 19360663]
5. Campbell DB, Sutcliffe JS, Ebert PJ, Militerni R, Bravaccio C, Trillo S, Elia M, Schneider C, Melmed R, Sacco R, Persico AM, Levitt P. A genetic variant that disrupts *MET* transcription is associated with autism. Proc Natl Acad Sci U S A. Nov 7; 2006 103(45):16834–16839. [PubMed: 17053076]
6. Campbell DB, D'Oronzio R, Garbett K, Ebert PJ, Mirnics K, Levitt P, Persico AM. Disruption of cerebral cortex MET signaling in autism spectrum disorder. Ann Neurol. Sep; 2007 62(3):243–250. [PubMed: 17696172]

7. Heuer L, Braunschweig D, Ashwood P, Van de Water J, Campbell D. Association of a *MET* genetic variant with autism-associated maternal autoantibodies to fetal brain proteins and cytokine expression. Transl Psychiatry. 2011; 1 2011/2010/2018/online.

8. Sheng L, Ding X, Ferguson M, McCallister M, Rhoades R, Maguire M, Ramesh A, Aschner M, Campbell D, Levitt P, Hood DB. Prenatal polycyclic aromatic hydrocarbon exposure leads to behavioral deficits and downregulation of receptor tyrosine kinase, MET. Toxicol Sci. Dec; 2010 118(2):625–634. [PubMed: 20889680]

9. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, Rauh V. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. Aug; 2009 124(2):e195–202. [PubMed: 19620194]

10. Perera FP, Wang S, Vishnevetsky J, Zhang B, Cole KJ, Tang D, Rauh V, Phillips DH. Polycyclic aromatic hydrocarbons-aromatic DNA adducts in cord blood and behavior scores in New York city children. Environ Health Persp. Aug; 2011 119(8):1176–1181.

11. Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. Environ Health Perspect. Jul; 2006 114(7):1119–1125. [PubMed: 16835068]

12. Bensen PE. A review of the development and application of the CA-LINE3 and 4 models. Atmos Environ. 1992; 26B:379–390.

Epidemiology. Author manuscript; available in PMC 2014 May 13.

Table

Crude and Adjusted[a] Associations of Air Pollution Exposure, *MET* rs1858830 Genotype, and Autism Spectrum Disorder Risk (n=407)

Exposure Quartile	*MET* Genotype	No. Autism Cases (n=251)	No. Controls (n=156)	Crude OR (95%CI)	aOR (95% CI)
Traffic-Related Air Pollution					
Top[b]	CC	18	4	2.9 (1.1–10.4)	2.9 (1.0–10.6)
	CG/GG	38	34	1.3 (0.78–2.3)	1.3 (0.73–2.2)
Bottom 3	CC	55	27	0.72 (0.43–1.2)	0.80 (0.47–1.4)
	CG/GG	140	91	1.00	1.00
$PM_{2.5}$					
Top[c]	CC	23	8	2.0 (0.88–4.9)	2.1 (0.92–5.4)
	CG/GG	33	30	1.7 (0.99–2.0)	1.7 (0.96–3.1)
Bottom 3	CC	55	22	0.75 (0.43–1.3)	0.82 (0.46–1.5)
	CG/GG	140	96	1.00	1.00
PM_{10}					
Top[d]	CC	24	6	2.9 (1.2–8.0)	3.2 (1.3–9.1)
	CG/GG	32	32	2.2 (1.3–4.0)	2.1 (1.2–3.9)
Bottom 3	CC	58	19	0.72 (0.41–1.3)	0.76 (0.43–1.4)
	CG/GG	137	99	1.00	1.00
Nitrogen Dioxide					
Top[e]	CC	21	4	3.4 (1.2–11.8)	3.6 (1.3–12.7)
	CG/GG	35	34	1.3 (0.74–2.2)	1.2 (0.71–2.1)
Bottom 3	CC	53	27	0.66 (0.38–1.1)	0.72 (0.41–1.3)
	CG/GG	142	91	1.00	1.00
Ozone					
Top[f]	CC	16	12	0.86 (0.39–1.9)	0.95 (0.42–2.2)
	CG/GG	40	26	1.3 (0.75–2.3)	1.2 (0.67–2.2)
Bottom 3	CC	47	23	0.99 (0.57–1.7)	1.0 (0.59–1.9)

Exposure Quartile	*MET* Genotype	No. Autism Cases (n=251)	No. Controls (n=156)	Crude OR (95%CI)	aOR (95% CI)
	CG/GG	178	95	1.00	1.00

[a] Models adjusted for child's sex, child's ethnicity (Hispanic vs. White, Black/Asian/Other vs. White), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 years vs. ≤35years), prenatal smoking (self-report of ever- vs. never-smoked while pregnant), and home ownership (owner vs. renter).

[b] ≥ 30.2 parts per billion.

[c] ≥ 16.0 microgram/meters cubed.

[d] ≥29.2 microgram/meters cubed.

[e] ≥17.5 parts per billion.

[f] ≥41.8 parts per billion.

Published in final edited form as:
JAMA Psychiatry. 2013 January ; 70(1): 71–77. doi:10.1001/jamapsychiatry.2013.266.

Traffic Related Air Pollution, Particulate Matter, and Autism

Dr. Heather E. Volk, PhD, MPH, **Messer. Fred Lurmann**, **Messer. Bryan Penfold**, **Dr. Irva Hertz-Picciotto, PhD**, and **Dr. Rob McConnell, MD**
Department of Preventive Medicine, Pediatrics, Zilkha Neurogenetic Institute, Keck School of Medicine, Children's Hospital Los Angeles, University of Southern California (Dr. Volk), Department of Public Health Sciences, University of California (Dr. Hertz-Picciotto), Sonoma Technology, Inc., (Messers Lurmann and Penfold), Department of Preventive Medicine, Keck School of Medicine, University of Southern California (Dr. McConnell)

Abstract

Context—Autism is a heterogeneous disorder with genetic and environmental factors likely contributing to its origins. Examination of hazardous pollutants has suggested the importance of air toxics in autism etiology, yet little research has examined local level air pollution associations using residence-specific exposure assignments.

Objective—To examine the relationship between traffic-related air pollution (TRP), air quality, and autism.

Design, Setting and Population—This study includes data on 279 autism cases and 245 typically developing controls enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study in California. The mother's address from the birth certificate and addresses reported from a residential history questionnaire were used to estimate exposure for each trimester of pregnancy and first year of life. TRP was assigned to each location using a line-source air-quality dispersion model. Regional air pollutant measures were based on the Environmental Protection Agency's Air Quality System data. Logistic regression models

Corresponding Author: Dr. Heather E. Volk, University of Southern California, 2001 N. Soto Street, MC9237, Los Angeles, CA 90089 (hvolk@usc.edu).
Reprint Requests: Heather E. Volk, PhD, MPH, University of Southern California, 2001 N. Soto Street, MC 9237, Los Angeles, CA 90089 (hvolk@usc.edu)

A portion of this research was presented at the International Meeting for Autism Research on May 14, 2011 in San Diego, California and at the meeting of the International Society for Environmental Epidemiology on September 16, 2011 in Barcelona, Spain.

The other authors declare no competing financial interests.

Author Contributions: Dr. Volk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Volk, McConnell
Acquisition of data: Lurmann, Penfold, Hertz-Picciotto
Analysis and interpretation of data: Volk, McConnell, Hertz-Picciotto, Lurmann
Drafting of the manuscript: Volk
Critical revision of the manuscript for important intellectual content: Volk, Hertz-Picciotto, McConnell, Lurmann, Penfold
Statistical analysis: Volk
Obtained funding: Hertz-Picciotto, McConnell, Volk
Study Supervision: Volk

Financial Disclosures: Fred Lurmann and Bryan Penfold are employed by Sonoma Technology Inc., Petaluma, CA. Rob McConnell has received support from an air quality violations settlement agreement between the South Coast Air Quality Management District, a California state regulatory agency, and BP. The other authors declare no competing financial interests.

compared estimated and measured pollutant levels for autism cases and typically developing controls.

Main Outcome Measures—Crude and multivariable-adjusted odds ratios (OR) for autism.

Results—Cases were more likely to live at residences in the highest quartile TRP exposure during pregnancy (OR=1.98, 95%CI 1.20–3.31) and the first year of life (OR=3.10, 1.76–5.57) compared to controls. Regional exposure measures of nitrogen dioxide (NO_2) and particulate matter less than 2.5 and 10 microns in diameter ($PM_{2.5}$ and PM_{10}) were also associated with autism during gestation (NO_2 OR=1.81/2SD, 95%CI 1.37–3.09; $PM_{2.5}$ OR=2.08/2SD, 95%CI 1.93–2.25; PM_{10} OR=2.17/2SD, 95%CI 1.49–3.16) and the first year of life (NO_2 OR=2.06, 95%CI 1.37–3.09; $PM_{2.5}$ OR=2.12, 95%CI 1.45–3.10; PM_{10} OR=2.14, 95%CI 1.46–3.12).

Conclusions—Exposure to TRP, NO_2, $PM_{2.5}$, and PM_{10} during pregnancy and the first year of life was associated with autism. Further epidemiological and toxicological examination of likely biological pathways will help determine whether these associations are causal.

Introduction

Autism spectrum disorders (ASDs) are a group of developmental disorders commonly characterized by problems in communication, social interaction, and repetitive behaviors or restricted interests.[1] While the severity of impairment for the ASDs varies across the spectrum (full syndrome autism being the most severe), the incidence rate of all ASDs is now reported to be as high as 1 in 110 children.[2] Emerging evidence suggests environment plays a role in autism, yet at this stage, only limited information is available as to what exposures are relevant, their mechanisms of action, stages of development in which they act, and then how to develop effective preventive measures.

Recently, air pollution has been examined as a potential risk factor for autism. Using the Environmental Protection Agency's (EPA) dispersion model-estimates of ambient concentrations of Hazardous Air Pollutants (HAPs), Windham and colleagues identified an increased autism risk based on exposure to diesel exhaust particles, metals (mercury, cadmium and nickel) and chlorinated solvents in Northern California census tracts.[3] Additional research using dispersion model-estimates of HAPs also reported associations between autism and air toxics at the birth residence of children from North Carolina and West Virginia.[4] These epidemiologic findings on autism are supported by additional research describing other physical and developmental effects of air pollution due to prenatal and early life exposure. For example, high levels of air pollutants have been associated with poor birth outcomes, immunologic changes, and decreased cognitive abilities.[5,6]

Recently, we reported an association between autism risk and early life residence within 309 meters of a freeway in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study.[7] The near source traffic-related air pollutant (TRP) mixture has large spatial variation, returning to near background daytime levels beyond this distance.[8,9] Here we report associations of autism with estimates of exposure to the mixture of TRP and with regional measures of nitrogen dioxide (NO_2), particulate matter < 2.5 μm aerodynamic diameter ($PM_{2.5}$), and particulate matter < 10 μm aerodynamic diameter (PM_{10}) in the CHARGE sample.

Methods

The CHARGE study is a population-based case-control study of preschool children. The study design is described in detail elsewhere.[10] Briefly, CHARGE subjects were between the ages of 24 and 60 months at the time of recruitment, lived with at least one English- or Spanish-speaking biologic parent, were born in California, and lived in one of the study catchment areas. Recruitment was facilitated by the California Department of Developmental Services (DDS), the Regional Centers with which they contract to coordinate services for persons with developmental disabilities, and referrals from the M.I.N.D. Institute clinic at the University of California, Davis (UCD) and from other research studies. Population-based controls were recruited from the sampling frame of birth files from the state of California, and were frequency matched by gender, age, and broad geographic area to the autism cases.

Each participating family was evaluated in person. Children with a previous diagnosis of autism were evaluated using the Autism Diagnostic Observation Schedules (ADOS) and parents were administered the Autism Diagnostic Interview-Revised (ADI-R).[11,12] Children with diagnosed developmental delay and general population controls were given the Social Communication Questionnaire (SCQ) to screen for the presence of autistic features.[13] If the SCQ score was 15 or greater, the child was then given the ADOS and the parent the ADI-R. In our study, autism cases were children with a diagnosis of full syndrome autism from both the ADOS and the ADI-R. All children were also assessed using the Mullen Scales of Early Learning (MSEL) and the Vineland Adaptive Behavior Scales (VABS) to collect information on motor skills, language, socialization, and daily living skills.[14,15] Controls were children sampled from the general population set who received a score less than 15 on the SCQ and who also showed no evidence of other types of delay (cognitive or adaptive).

Parents were interviewed to obtain demographic and medical information, and, among other factors, residential histories. Race/ethnicity data were collected by self-report in categories defined by the US Census (Table 1). The residential data captured addresses and corresponding dates the mother and child lived at each location beginning 3 months before conception and extending to the most recent place of residence. Further details about the collection of clinical and exposure data have been previously reported.[10]

To obtain model-based estimates of TRP exposure, we applied the CALINE4 line-source air-quality dispersion model.[16] The dispersion model was used to estimate average concentrations for the specific locations and time periods (trimesters of gestation and first year of life) for each subject. The principal model inputs are roadway geometry, link-based traffic volumes, period-specific meteorological conditions (wind speed and direction, atmospheric stability, and mixing heights), and vehicle emission rates. Detailed roadway geometry data and annual average daily traffic counts were obtained from Tele Atlas/ Geographic Data Technology (GDT) in 2005. These data represent an integration of state-, county-, and city-level traffic counts collected between 1995 and 2000. Because our period of interest was 1997 to 2008, the counts were scaled to represent individual years based on estimated growth in county average vehicle-miles-traveled (VMT) data.[17] Traffic counts were assigned to roadways based on location and street names. Traffic volumes on roadways

without count data (mostly small roads) were estimated based on median volumes for similar class roads in small geographic regions. Meteorological data from 56 local monitoring stations were matched to the dates and locations of interest. Vehicle fleet average emission factors were based on the California Air Resource Board's EMFAC2007 (version 2.3) model. Annual average emission factors were calculated by year (1997–2008) for travel on freeways (65 mph), state highways (50 mph), arterials (35 mph), and collectors (30 mph). We used the CALINE4 model to estimate locally varying ambient concentrations of nitrogen oxides (NO_x) contributed by freeways, non-freeways, and all roads located within 5 km of each child's home. Previously, we have used the CALINE4 model to estimate concentrations of other traffic-related pollutants, including elemental carbon and carbon monoxide; and found that they were almost perfectly correlated (around 0.99) with estimates for nitrogen oxides. Thus, our model-based concentrations should be viewed as an indicator of the TRP mixture rather than any pollutant specifically.

A second approach was to use the regional air quality data for the exposure assignments for $PM_{2.5}$, PM_{10}, ozone (O_3) and NO_2. These were derived from the US EPA's Air Quality System (AQS) data (www.epa.gov/ttn/airs/airsaqs) supplemented by USC's Children's Health Study (CHS) data for 1997–2009.[18] CHS continuous PM data were used for a given monitoring station when no Federal Reference/Equivalent Method data for PM were available from AQS. The monthly air quality data from monitoring stations located within 50 km of each residence were made available for spatial interpolation of ambient concentrations. The spatial interpolations were based on inverse distance-squared weighting (IDW2) of data from up to four closest stations located within 50 km of each participant residence; however, if one or more stations were located within 5 km of a residence then only data from the stations within 5 km were used for the interpolation. Because special studies have shown large offshore to onshore pollutant gradients along the southern California coast, the interpolations were carried out with pseudo-stations, or theoretical locations used for estimating pollution gradients from extant data when geography did not permit observed data, located ~ 20–40 km offshore that had background concentrations based on long-term measurements (1994–2003) at clean coastal locations (i.e., Lompoc, CA).

Periods and locations relevant to the modeled traffic exposure were identified based on dates and addresses recorded on the birth certificate and from the residential history questionnaire. The birth certificate addresses corresponded to the mother's residence at the time of child's birth while the residential history captures both mother's residences during pregnancy (required for estimation of prenatal exposure) and child's residences after birth through the time of study enrollment. We determined the conception date for each child using gestational age from ultrasound measurements or the date of last menstrual period, as determined from prenatal records. We used these locations and dates to estimate exposure for the first year of life, the entire pregnancy period, and each trimester of pregnancy. When more than 1 address fell into a time interval, we created a weighted average to reflect the exposure level of the participant across the time of interest taking into account changes in residence. TRP was determined based on the required inputs reflecting change in each address over the study period. For the regional pollutant measures, we assigned $PM_{2.5}$, PM_{10}, and NO_2 measurements based on average concentrations for the time period of

interest. For O_3, we calculated the averages for the period of interest based on the 1000–1800 hours (reflecting the high 8 hour daytime) average. Based on these methods, we were able to assign TRP estimates and regional pollutant measures for 524 mother-child pairs.

Spearman correlations were calculated pairwise between TRP estimates and regional pollution measures for pregnancy and the first year of life to assess independence of these exposure metrics. We used logistic regression to examine the association between exposure to traffic-related air pollution and autism risk. Models of autism risk as a function of TRP exposure levels from all road types were fitted separately for each time period. Categories of exposure were formed based on quartiles of the TRP distribution for all pregnancy as this provided the most comprehensive data for each child. Levels of regional pollutants were examined as continuous variables and effect estimates scaled to twice the standard deviation of the distribution for the all pregnancy estimates. When levels of correlation permitted, we examined both TRP and regional pollutants in a single model. Pertinent covariates were included in each model to adjust for potential confounding due to socio-demographic and lifestyle characteristics. We included children's gender and ethnicity, maximum education level of the parents, maternal age, and maternal smoking during pregnancy as described previously.[7] To examine if our findings were affected by living in an urban or rural area, we included population density obtained from Environmental Systems Research Institute Inc.'s 2008 estimates of people per square meter (p/m^2) using ArcGIS software (version 9.2). We used the United States Census Bureau cut off of 2,500 p/m^2 to categorize population density into urban vs. rural areas and included this variable as a covariate in analysis of air pollution effects from the first year of life since these residences were the most recent recorded.

We also fitted logistic additive models to evaluate the relationship between autism and TRP. These models used the smoothing spline with three degrees of freedom for continuous TRP and used the same adjustment variables as in the linear logistic models described above. Statistical tests were conducted using an alpha level of 0.05 and 95% confidence limits were used to measure precision. All analyses were conducted using the R package version 2.9.2 (www.r-project.org). Institutional review boards of the University of Southern California and UCD approved the research.

Results

Children in this study were predominantly male (84%) and most were non-Hispanic Caucasian (50%) or Hispanic (30%). No differences were found between cases and controls for any demographic, socioeconomic, or lifestyle variables we examined (eTable 1). Details regarding the exposure distributions are presented in eFigures 1a and 1b. Spearman correlations calculated for the first year of life and pregnancy time periods are presented in Table 1. During pregnancy and the first year TRP was moderately correlated with $PM_{2.5}$ and PM_{10}, highly correlated with NO_2, but inversely correlated with O_3. Among the regional pollutant measures, $PM_{2.5}$ and PM_{10} were nearly perfectly correlated and both were highly correlated with NO_2. Correlations with O_3 were low and often negative, demonstrating an inverse relationship. We also examined correlations of each pollutant across time periods and high correlations were identified.

Traffic Related Air Pollution Exposure

Increased autism risk was associated with exposure to traffic related air pollution during the first year of life. Children residing in homes with the highest levels of modeled TRP were three times as likely to have autism compared to children with the lowest exposure (Table 2). Exposure in the middle quartile groups (2nd and 3rd) was not associated with an increased risk of autism. In our analysis including population density, this association with the highest quartile of exposure was still evident (OR=3.48, 95%CI 1.81–6.83) and living in an urban area, compared to rural, was not associated with autism (OR=0.86, 95%CI 0.56–1.31). When we examined TRP exposures during pregnancy, the highest quartile was also associated with autism risk (OR=1.98, 95%CI 1.20–3.31) compared to the lowest quartile. We further divided the pregnancy into three trimesters and modeled TRP based on these intervals. During all three trimesters of pregnancy, we found associations with the highest quartile of exposure (≥31.8 ppb), compared to the lowest quartile (≤9.7 ppb), and autism (Table 2). Inclusion of demographic and socioeconomic variables in the models did not greatly alter these associations (Table 2).

Since our quartile-based categories indicated that there is a threshold upon which TRP exposure is detrimental, we also examined the relationship of TRP exposure and autism using smoothed models for the first year of life and all of pregnancy. An increasing probability of autism was seen with increasing TRP estimates, with the odds reaching a plateau when TRP estimates were above 25–30 ppb (Figure 1).

Regional Air Pollutant Exposure

Higher levels of exposure to $PM_{2.5}$, PM_{10}, and NO_2 based on the EPA's regional air quality monitoring program were associated with increased risk of autism (Table 3). Specifically for an 8.7 unit increase ($\mu g/m^3$) in $PM_{2.5}$ (corresponding to twice the standard deviation of the $PM_{2.5}$ distribution) exposure during the first year of life, children were 2.12 times more likely to have autism. Increases were also present for pregnancy and trimester-specific estimates of $PM_{2.5}$ with the smallest effects present in the first trimester. For PM_{10}, a 14.6 unit increase ($\mu g/m^3$) during the first year was associated with twice the risk of autism (Table 3). Associations were present for pregnancy and each trimester with the first trimester having the smallest magnitude. We did not find associations between levels of regional O_3 and autism. Regional NO_2 exposure during the first year was associated with a two-fold autism risk. Similar effects were identified for NO_2 exposure during pregnancy. While exposure during each of the three trimesters was associated with autism, effects of the first trimester were the smallest. For all regional pollutant measures, adjustment for demographic and socioeconomic variables did not alter the associations. As with TRP, when we included population density in the models including exposure during the first year of life associations with $PM_{2.5}$, PM_{10}, and NO_2 did not change, nor did they change when living in an urban area vs. a rural area was included (data not shown).

TRP, $PM_{2.5}$, and PM_{10}

Because pairwise correlations between TRP and $PM_{2.5}$ and TRP and PM_{10} were moderate, we included both in models to examine if local pollution estimates (TRP) and regional pollution measures ($PM_{2.5}$ and PM_{10}) were independently associated with autism. In these

analyses, we included the same set of covariates described above in the single pollutant analysis. When examined in the same model, both the top quartile of TRP (OR=2.37, 95%CI 1.28–4.45) and $PM_{2.5}$ (OR=1.58/2SD, 95%CI 1.03–2.42) exposure during the first year of life remained associated with autism. Examining both TRP and PM_{10}, we found that the top quartile of TRP (OR=2.36, 95%CI 1.28–4.43) and PM_{10} (OR=1.61, 95%CI 1.06–2.47) remained associated with autism. For all pregnancy, we found that both the top quartile of TRP (OR=2.42, 95%CI 1.32–4.50) and $PM_{2.5}$ (OR=1.60, 95%CI 1.07–2.40) were associated with autism when examined in the same model. Similarly, both the top quartile of TRP (OR=2.33, 95%CI 1.27–4.36) and PM_{10} (OR=1.68, 95%CI 1.11–2.53) remained associated with autism when examined jointly.

Discussion

This study found that local estimates of TRP and regional measures of $PM_{2.5}$, PM_{10}, and NO_2 at residences were higher in children with autism. The magnitude of these associations appear to be most pronounced during late gestation and early life, though it was not possible to adequately distinguish a period critical to exposure. Children with autism were three times as likely to have been exposed during the first year of life to higher modeled traffic-related air pollution as compared with typically developing controls. Similarly, exposure to TRP during pregnancy was also associated with autism. Examination of TRP using an additive logistic model demonstrated a potential threshold near 25–30ppb beyond which the probability of autism did not increase. Exposure to high levels of regional $PM_{2.5}$, PM_{10}, and NO_2 were also associated with autism. When we examined $PM_{2.5}$ or PM_{10} exposure jointly with TRP, both regional and local pollutants remained associated with autism though the magnitude of effects decreased.

We previously reported an association between living near a freeway, based on the location of the birth and third trimester address, and autism.[7] That result relied on simple distance metrics as a proxy for exposure to traffic related air pollution. The present study builds on that result, demonstrating associations with both regional particulate and NO_2 exposure and to dispersion-modeled exposure to the near-roadway traffic mixture accounting for traffic volume, fleet emission factors and wind speed and direction, in addition to traffic proximity. The results provide more convincing evidence that exposure to local air pollution from traffic may increase risk of autism. Demographic or socio-economic factors did not explain these associations.

Toxicological and genetic research suggests possible biologically plausible pathways to explain these results. Concentrations of many air pollutants, including diesel exhaust particles (DEP) and other PM constituents, are increased near freeways and other major roads, and DEP and the polycyclic aromatic hydrocarbons (PAHs) commonly present in DEP affect brain function and activity in toxicological studies. [19–23] PAHs have been shown to reduce expression of the *MET receptor tyrosine kinase* gene, which is important in early life neurodevelopment and is markedly reduced in autistic brains.[24,25] Other research indicates that TRPs induce inflammation and oxidative stress after both short term and long term exposures, processes which mediate effects of air pollution on respiratory and cardiovascular disease and other neurological outcomes.[26–29] Data examining biomarkers

suggests that oxidative stress and inflammation may also be involved in the pathogenesis of autism.[30–33]

Emerging evidence suggests that systemic inflammation may also result in damage to endothelial cells in the brain and compromise the blood-brain barrier.[29] Systemic inflammatory mediators may cross the blood-brain barrier, activating brain microglia, and peripheral monocytes may migrate into the pool of microglia.[34–36] In addition, ultrafine particles ($PM_{0.1}$) may penetrate cellular membranes.[37,38] These particles translocate indirectly through the lungs and from the systemic circulation or directly via the nasal mucosa and the olfactory bulb into the brain.[39,40] Toxicity may be mediated by physical properties of PM, or by the diverse mixture of organic compounds, including PAHs, and oxidant metals adsorbed to the surface.[29] Neurodevelopmental effects of PAHs may be mediated by aryl hydrocarbon hydroxylase induction in placenta, decreased exchange of oxygen secondary to disruption of placental growth factor receptors, endocrine disruption, activation of apoptotic pathways, inhibition of the brain antioxidant-scavenging system resulting in oxidative stress, or epigenetic effects.[21]

This study draws on a rich record of residential locations of typically developing children and children with autism across California, allowing us to assign modeled pollutant exposures for developmentally relevant time points. However, our results could also be affected by unmeasured confounding factors associated with both autism and traffic related air pollution exposure. While we did not find that including demographic or socio-economic variables altered our estimates of effect, confounding by other factors could still occur. These might include lifestyle, nutritional, or other residential exposures, if they were associated with TRP or PM. We have also not explored indoor sources of pollution, such as indoor NO or second-hand tobacco smoke, though prenatal smoking was examined and did not influence the associations of ambient pollution with autism. Additionally, confounding could have occurred if proximity to diagnosing physicians or treatment centers were also associated with exposure. We included population density as an adjustment in an analysis using estimates from the first year of life to examine the sensitivity of our results to urban or rural locations, for which population density is a surrogate. We did not find that living in a more densely populated area altered the association between autism risk and TRP or regional pollutants. Despite our attempts to use a residential history to examine specific time windows of vulnerability, incorporation of meteorology into our TRP models, and inclusion of pollutants with seasonal variation, we are currently unable to disentangle effects trimester-specific effects or during the first year of life because of the high correlation across these time periods.

Exposure to TRP, PM, and NO2 were associated with increased autism risk. These effects were observed from measures of air pollution with variation on both local and regional levels suggesting the need for further study to understand both individual pollutant contributions and the effects of pollutant mixtures on disease. Research on pollutant exposure effects and their interaction with susceptibility factors may lead to identification of biologic pathways activated in autism and improved prevention and therapeutic strategies. While additional research and replication of these findings is needed, the public health

implications of these findings are large because air pollution exposure is common and may have lasting neurological effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by NIEHS grants ES019002, ES013578, ES007048, ES11269, ES015359, ES016535, ES011627, EPA Star-R-823392, EPA Star-R-833292, and the MIND Institute matching funds and pilot grant program. These funders did not in any way influence the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Fred Lurmann and Bryan Penfold are employed by Sonoma Technology Inc., Petaluma, CA. Rob McConnell has received support from an air quality violations settlement agreement between the South Coast Air Quality Management District, a California state regulatory agency, and BP.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: American Psychiatric Association; 2000. Text Revision
2. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill Summ. 2009; 58(10):1–20.
3. Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. Environ Health Perspect. 2006; 114(9):1438–44. [PubMed: 16966102]
4. Kalkbrenner AE, Daniels JL, Chen JC, Poole C, Emch M, Morrissey J. Perinatal Exposure to Hazardous Air Pollutants and Autism Spectrum Disorders at Age 8. Epidemiology. 2010; 20(7): 615–24.
5. Currie J, Neidell M, Schmieder JF. Air pollution and infant health: Lessons from New Jersey. J Health Econ. 2009; 28(3):688–703. [PubMed: 19328569]
6. Hansen CA, Barnett AG, Pritchard G. The effect of ambient air pollution during early pregnancy on fetal ultrasonic measurements during mid-pregnancy. Environ Health Perspect. 2008; 116(3):362–9. [PubMed: 18335104]
7. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential Proximity to Freeways and Autism in the CHARGE study. Environ Health Perspect. 2011; 119(6):873–7. [PubMed: 21156395]
8. Zhu YF, Hinds WC, Kim S, Sioutas C. Concentration and size distribution of ultrafine particles near a major highway. Journal of the Air & Waste Management Association. 2002; 52:1032–1042. [PubMed: 12269664]
9. Zhu Y, Hinds WC, Kim S, Shen S, Sioutas C. Study of ultrafine particles near a major highway with heavy-duty diesel traffic. Atmospheric Environment. 2002; 36(27):4323–4335.
10. Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. Environ Health Perspect. 2006; 114(7):1119–25. [PubMed: 16835068]
11. Le Couteur, A.; Lord, C.; Rutter, M. Autism Diagnostic Interview-Revised (ADI-R). Los Angeles: Western Psychological Services; 2003.
12. Lord, C.; Rutter, M.; DiLavore, P.; Risi, S. Autism Diagnostic Observation Schedule Manual. Los Angeles: Western Psychological Services; 2003.
13. Rutter, M.; Bailey, A.; Lord, C. A Social Communication Questionnaire (SCQ). Los Angeles: Western Psychological Services; 2003.

14. Sparrow, S.; Cicchettim, D.; Balla, D. Vineland Adaptive Behavior Scales Interview Edition Expanded Form Manual. Circle Pines, MN: American Guidance Services Inc; 1984.
15. Mullen, E. Mullen Scales of Early Learning. Circle Pines, MN: American Guidance Services Inc; 1995.
16. Bensen PE. A review of the development and application of the CA-LINE3 and 4 models. Atmos Environ. 1992; 26B:379–390.
17. California Department of Transportation. California motor vehicle stock, travel and fuel forecast. 2004.
18. Alcorn SH, Lurmann FW. Southern California Children's Health Study exposure database. 2003
19. Ntziachristos L, Geller MD, Sioutas C. Particle concentration and characteristics near a major freeway with heavy-duty diesel traffic. Environ Sci Technol. 2007; 41(7):2223–2230. [PubMed: 17438767]
20. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, Hoepner L, Barr D, Tu YH, Camann D, Kinney P. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006; 114(8):1287–92. [PubMed: 16882541]
21. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, Rauh V. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. 2009; 124(2):e195–202. [PubMed: 19620194]
22. Hougaard KS, Jensen KA, Nordly P, Taxvig C, Vogel U, Saber AT, Wallin H. Effects of prenatal exposure to diesel exhaust particles on postnatal development, behavior, genotoxicity and inflammation in mice. Part Fibre Toxicol. 2008; 5:3. [PubMed: 18331653]
23. Brown LA, Khousbouei H, Goodwin JS, Irvin-Wilson CV, Ramesh A, Sheng L, McCallister MM, Jiang GC, Aschner M, Hood DB. Down-regulation of early ionotrophic glutamate receptor subunit developmental expression as a mechanism for observed plasticity deficits following gestational exposure to benzo(a)pyrene. Neurotoxicology. 2007; 28(5):965–78. [PubMed: 17606297]
24. Levitt P, Campbell DB. The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders. J Clin Invest. 2009; 119(4):747–54. [PubMed: 19339766]
25. Campbell DB, D'Oronzio R, Garbett K, Ebert PJ, Mirnics K, Levitt P, Persico AM. Disruption of cerebral cortex MET signaling in autism spectrum disorder. Ann Neurol. 2007; 62(3):243–50. [PubMed: 17696172]
26. Castro-Giner F, Kunzli N, Jacquemin B, Forsberg B, de Cid R, Sunyer J, Jarvis D, Briggs D, Vienneau D, Norback D, Gonzalez JR, Guerra S, Janson C, Anto JM, Wjst M, Heinrich J, Estivill X, Kogevinas M. Traffic-related air pollution, oxidative stress genes, and asthma (ECHRS). Environ Health Perspect. 2009; 117(12):1919–24. [PubMed: 20049212]
27. Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. Lancet. 2004; 363(9403):119–25. [PubMed: 14726165]
28. Kunzli N, Jerrett M, Garcia-Esteban R, Basagana X, Beckermann B, Gilliland F, Medina M, Peters J, Hodis HN, Mack WJ. Ambient air pollution and the progression of atherosclerosis in adults. PLoS One. 5(2):e9096. [PubMed: 20161713]
29. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci. 2009; 32(9):506–16. [PubMed: 19716187]
30. Enstrom A, Krakowiak P, Onore C, Pessah IN, Hertz-Picciotto I, Hansen RL, Van de Water JA, Ashwood P. Increased IgG4 levels in children with autism disorder. Brain Behav Immun. 2009; 23(3):389–95. [PubMed: 19136055]
31. James SJ, Rose S, Melnyk S, Jernigan S, Blossom S, Pavliv O, Gaylor DW. Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. FASEB J. 2009; 23(8):2374–83. [PubMed: 19307255]
32. Li X, Chauhan A, Sheikh AM, Patil S, Chauhan V, Li XM, Ji L, Brown T, Malik M. Elevated immune response in the brain of autistic patients. J Neuroimmunol. 2009; 207(1–2):111–6. [PubMed: 19157572]

33. Ashwood P, Enstrom A, Krakowiak P, Hertz-Picciotto I, Hansen RL, Croen LA, Ozonoff S, Pessah IN, Van de Water J. Decreased transforming growth factor beta1 in autism: a potential link between immune dysregulation and impairment in clinical behavioral outcomes. J Neuroimmunol. 2008; 204(1–2):149–53. [PubMed: 18762342]
34. Nguyen MD, Julien JP, Rivest S. Innate immunity: the missing link in neuroprotection and neurodegeneration? Nat Rev Neurosci. 2002; 3(3):216–27. [PubMed: 11994753]
35. Banks WA, Farr SA, Morley JE. Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation. 2002; 10(6):319–27. [PubMed: 12907838]
36. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. J Neurosci. 2009; 29(7):2089–102. [PubMed: 19228962]
37. Geiser M, Rothen-Rutishauser B, Kapp N, Schurch S, Kreyling W, Schulz H, Semmler M, Im Hof V, Heyder J, Gehr P. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. Environ Health Perspect. 2005; 113(11):1555–60. [PubMed: 16263511]
38. Rothen-Rutishauser B, Mueller L, Blank F, Brandenberger C, Muehlfeld C, Gehr P. A newly developed in vitro model of the human epithelial airway barrier to study the toxic potential of nanoparticles. ALTEX. 2008; 25(3):191–6. [PubMed: 18841315]
39. Campbell A, Araujo JA, Li H, Sioutas C, Kleinman M. Particulate matter induced enhancement of inflammatory markers in the brains of apolipoprotein E knockout mice. J Nanosci Nanotechnol. 2009; 9(8):5099–104. [PubMed: 19928188]
40. Oberdorster G, Elder A, Rinderknecht A. Nanoparticles and the brain: cause for concern? J Nanosci Nanotechnol. 2009; 9(8):4996–5007. [PubMed: 19928180]

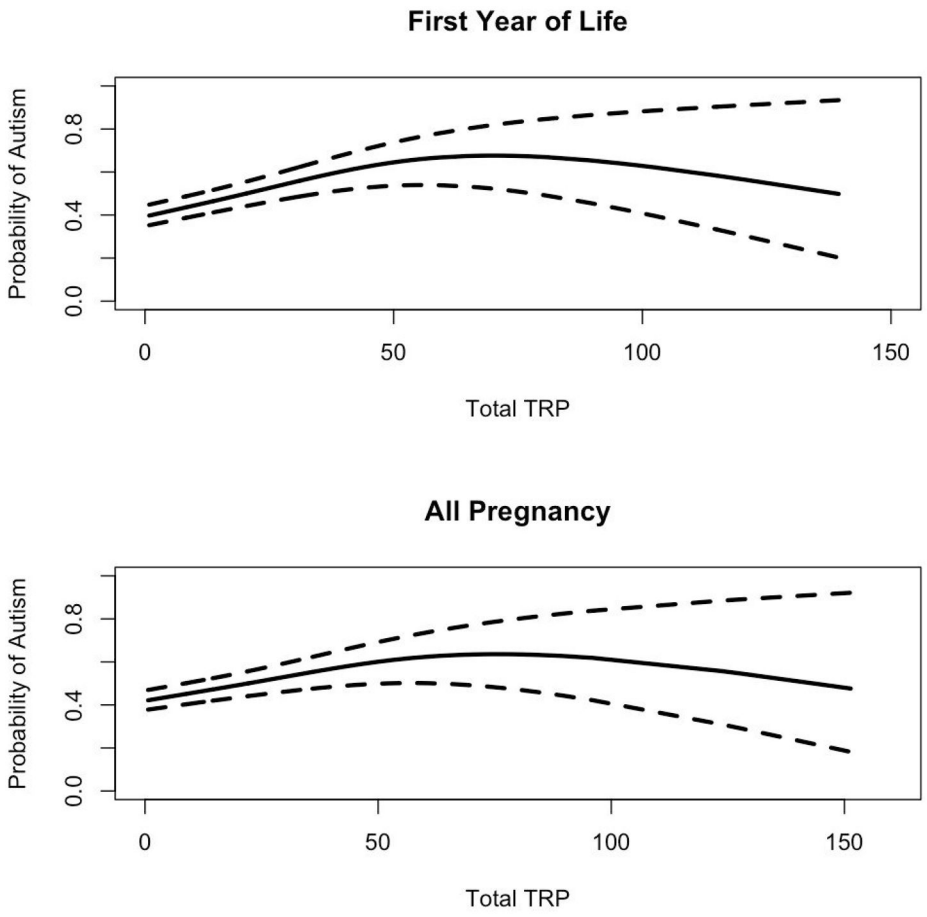


Figure 1.

Probability of autism by increasing level of traffic related air pollution (TRP) exposure for the first year of life and pregnancy. Dotted lines indicate 95% confidence interval.

Table 1

Spearman correlations (r) of traffic related pollution (TRP) and regional pollutants (N=524)*. Light grey shading reflects correlations across pollutants within pregnancy. Dark grey shading reflects correlations across pollutants within the first year of life. Values reported in the white boxes report correlations of the same pollutant across time periods.

	All Pregnancy				
	TRP	**$PM_{2.5}$**	**PM_{10}**	**Ozone**	**Nitrogen Dioxide**
TRP	0.92	0.36	0.33	−0.36	0.60
$PM_{2.5}$	0.25	0.67	0.77	−0.11	0.63
PM_{10}	0.27	0.84	0.82	0.13	0.66
Ozone	−0.31	0.26	0.27	0.74	−0.29
Nitrogen Dioxide	0.58	0.60	0.64	−0.19	0.89
	Year 1				

*All correlation measures were statistically significant ($p<0.05$).

$PM_{2.5}$ = particulate matter < 2.5μm aerodynamic diameter, PM_{10} = particulate matter < 10μm aerodynamic diameter.

Table 2

Odds ratios (OR) and 95% confidence intervals for autism, by quartile** of modeled traffic related air pollution (TRP) exposure from all road types (N=524).

		4th quartile	3rd quartile	2nd quartile
First Year of Life	**Crude**	2.97 (1.71–5.27)	1.00 (0.63–1.60)	0.88 (0.55–1.42)
	Adjusted*	3.10 (1.76–5.57)	1.00 (0.62–1.62)	0.91 (0.56–1.47)
All Pregnancy	**Crude**	1.99 (1.22–3.28)	1.10 (0.67–1.78)	1.20 (0.74–1.95)
	Adjusted*	1.98 (1.20–3.31)	1.09 (0.67–1.79)	1.26 (0.77–2.06)
First Trimester	**Crude**	1.91 (1.67–3.14)	1.28 (0.80–2.06)	1.28 (0.77–2.14)
	Adjusted*	1.85 (1.11–3.08)	1.28 (0.79–2.08)	1.28 (0.77–2.15)
Second Trimester	**Crude**	1.69 (1.04–2.78)	1.15 (0.71–1.87)	0.89 (0.54–1.47)
	Adjusted*	1.65 (1.00–2.74)	1.13 (0.69–1.84)	0.90 (0.54–1.49)
Third Trimester	**Crude**	2.04 (1.25–3.38)	0.92 (0.57–1.48)	1.12 (0.68–1.84)
	Adjusted*	2.10 (1.27–3.51)	0.91 (0.56–1.46)	1.17 (0.71–1.93)

* Model adjusted for child male gender, child ethnicity (Hispanic vs. White, Black/Asian/Other vs. White), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 years vs. ≤ 35years), and prenatal smoking (self report of ever vs. never smoked while pregnant).

** Quartile cut points correspond to TRP levels of 31.8 ppb or greater (4th quartile), 16.9–31.8 ppb (3rd quartile), and 9.7–16.9 ppb (2nd quartile), compared to 9.7 ppb or less (1st quartile, reference group).

Table 3

Odds ratios (OR) and 95% confidence intervals for autism based on continuous regional pollutant exposure (N=524)**.

		Regional Pollutant			
		$PM_{2.5}$	**PM_{10}**	**O_3**	**Nitrogen Dioxide**
First Year	**Crude**	2.14 (1.48–3.09)	2.14 (1.47–3.10)	1.15 (0.72–1.84)	2.06 (1.39–3.06)
	Adjusted*	2.12 (1.45–3.10)	2.14 (1.46–3.12)	1.15 (0.72–1.86)	2.06 (1.37–3.09)
All Pregnancy	**Crude**	2.11 (1.46–3.03)	2.17 (1.50–3.13)	1.08 (0.76–1.52)	1.82 (1.26–2.64)
	Adjusted*	2.08 (1.93–2.25)	2.17 (1.49–3.16)	1.09 (0.76–1.55)	1.81 (1.23–2.65)
First Trimester	**Crude**	1.24 (0.99–1.56)	1.47 (1.10–1.98)	1.07 (0.86–1.33)	1.47 (1.07–2.01)
	Adjusted*	1.22 (0.96–1.53)	1.44 (1.07–1.96)	1.08 (0.86–1.35)	1.44 (1.05–1.20)
Second Trimester	**Crude**	1.50 (1.16–1.93)	1.82 (1.35–2.45)	1.03 (0.84–1.27)	1.62 (1.17–2.25)
	Adjusted*	1.48 (1.40–1.57)	1.83 (1.35–2.47)	1.04 (0.84–1.29)	1.61 (1.15–2.25)
Third Trimester	**Crude**	1.39 (1.11–1.75)	1.61 (1.21–2.13)	1.03 (0.84–1.27)	1.65 (1.19–2.27)
	Adjusted*	1.40 (1.11–1.77)	1.61 (1.20–2.14)	1.03 (0.83–1.26)	1.64 (1.18–2.29)

*$PM_{2.5}$ = particulate matter < 2.5μm aerodynamic diameter, PM_{10} = particulate matter < 10μm aerodynamic diameter. Models adjusted for child male gender, child ethnicity (Hispanic vs. White, Black/ Asian/Other vs. White), maximum education of parents (parent with highest of four levels: college degree or higher vs. some high school, high school degree, or some college education), maternal age (>35 years vs. ≤ 35years), and prenatal smoking (self report of ever vs. never smoked while pregnant).

**Regional pollution effects reflect risk of autism based on 2 standard deviations from the mean value, specifically per increase of 8.7 $\mu g/m^3$ $PM_{2.5}$, 14.6 $\mu g/m^3$ PM_{10}, 14.1 ppb Nitrogen Dioxide, and 16.1 ppb Ozone.

HHS Public Access

Author manuscript

JAMA Intern Med. Author manuscript; available in PMC 2017 May 10.

Published in final edited form as:

JAMA Intern Med. 2016 September 01; 176(9): 1334–1343. doi:10.1001/jamainternmed.2016.2436.

Asthma Exacerbations and Unconventional Natural Gas Development in the Marcellus Shale

Sara G. Rasmussen, MHS[1], **Elizabeth L. Ogburn, PhD**[2], **Meredith McCormack, MD**[3], **Joan A. Casey, PhD**[4], **Karen Bandeen-Roche, PhD**[2], **Dione G. Mercer, BS**[5], and **Brian S. Schwartz, MD,MS**[1,3,5]

[1]Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[2]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[3]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

[4]Robert Wood Johnson Foundation Health and Society Scholars Program, UC San Francisco and UC Berkeley, California, USA

[5]Center for Health Research, Geisinger Health System, Danville, Pennsylvania, USA

Abstract

Importance—Asthma is common and can be exacerbated by air pollution and stress. Unconventional natural gas development (UNGD) has community and environmental impacts. In Pennsylvania, development began in 2005 and by 2012, 6,253 wells were drilled. There are no prior studies of UNGD and objective respiratory outcomes.

Objective—To evaluate associations between UNGD and asthma exacerbations.

Design—A nested case-control study comparing asthma patients with exacerbations to asthma patients without exacerbations from 2005–12.

Setting—The Geisinger Clinic, which provides primary care services to over 400,000 patients in Pennsylvania.

Participants—Asthma patients aged 5–90 years (n = 35,508) were identified in electronic health records; those with exacerbations were frequency-matched on age, sex, and year of event to those without.

Corresponding author: Brian S. Schwartz, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Room W7041, Baltimore, MD, 21205. bschwar1@jhu.edu.

Additional Contributions: We thank Joseph J. DeWalle, BS, Jennifer K. Irving, BA, and Joshua M. Crisp, BS (Geisinger Center for Health Research) for patient geocoding and assistance in assembling the UNGD dataset; SkyTruth in Shepherdstown, WV for the well pad data; Kirsten Koehler, PhD (JHSPH) for assistance with the temperature data; Kara Rudolph, PhD, MHS (Robert Wood Johnson Foundation Health and Society Scholars Program, UC San Francisco and UC Berkeley) for the code for the unmeasured confounder graphs; and Jonathan S. Pollak, MPP (JHSPH) for identifying the asthma patients from the general Geisinger population. All except KK and KR received compensation for their contributions.

We declare that we have no conflicts of interest.

Exposure(s)—On the day before each patient's index date (cases: date of event or medication order; controls: contact date), we estimated UNGD activity metrics for four phases (pad preparation, drilling, stimulation ["fracking"], and production) using distance from the patient's home to the well, well characteristics, and the dates and durations of phases.

Main Outcome(s) and Measure(s)—We identified mild, moderate, and severe asthma exacerbations (new oral corticosteroid medication order, emergency department encounter, and hospitalization, respectively).

Results—We identified 20,749 mild, 1,870 moderate, and 4,782 severe asthma exacerbations, and frequency-matched these to 18,693, 9,350, and 14,104 control index dates, respectively. In three-level adjusted models, there was an association between the highest group of the activity metric for each UNGD phase compared to the lowest group for 11 out of 12 UNGD-outcome pairs (odds ratios [95% CI] ranged from 1.5 [1.2–1.7] for the association of the pad metric with severe exacerbations to 4.4 [3.8–5.2] for the association of the production metric with mild exacerbations). Six of the 12 UNGD-outcome associations had increasing odds ratios across quartiles. Our findings were robust to increasing levels of covariate control and in sensitivity analyses that included evaluation of some possible sources of unmeasured confounding.

Conclusions and Relevance—Residential UNGD activity metrics were statistically associated with increased odds of mild, moderate, and severe asthma exacerbations. Whether these associations are causal awaits further investigation, including more detailed exposure assessment.

INTRODUCTION

Asthma is a common, chronic disease – in 2010, 25.7 million people in the United States had asthma, a prevalence of 8.4%.[1] Asthma is characterized by variable and recurring symptoms (including cough, wheezing, shortness of breath, and chest tightness), reversible airflow obstruction, bronchial hyper-responsiveness, and underlying inflammation.[2,3] In 2009, there were 11.8 million outpatient visits, 2.1 million emergency department visits, and 479,300 hospitalizations for asthma in the US.[1]

Outdoor air pollution is a recognized cause of asthma exacerbations. A large body of literature links asthma exacerbations to exposure to air pollutants, including ozone, particulate matter, nitrogen dioxide, and sulfur dioxide,[2,4] and exposure to even low levels of these pollutants has been associated with asthma hospitalizations, emergency department visits, and rescue medication use, with latency between 0 and 5 days.[5–11] Stress at the individual and community levels is also associated with asthma exacerbations.[12] Psychosocial stress can modify the effects of environmental triggers[13] and is associated with worse asthma control and medication aderence.[14]

Unconventional natural gas development (UNGD) has recently become a major energy source domestically and worldwide. Pennsylvania has proceeded with UNGD rapidly – between the mid-2000s and 2012, 6,253 wells were drilled. In contrast, New York and Maryland, also in the Marcellus shale, have not developed.[15,16] Despite calls for research on the health effects of the industry, there are few published studies of public health impacts of UNGD.[17,18]

The first step of UNGD is well pad preparation, lasting about 30 days, during which 3–5 acres are cleared and materials are brought to the site.[19] Drilling begins on the spud date and typically lasts up to a month as a well is drilled vertically 2,000–3,000 meters and horizontally 600–3,000 meters.[19] After drilling is completed, the horizontal portion is perforated. Stimulation, also called hydraulic fracturing or "fracking," follows, lasts around a week, and requires 11–19 million liters of water, sand, and chemical additives (e.g., friction reducers, biocides, gelling agents).[19,20] Development to this point requires over 1,000 truck trips per well.[19] After stimulation, gas production begins. The Pennsylvania Department of Environmental Protection (PA DEP) requires companies to submit documentation at most of these stages of well development.[21]

UNGD has been associated with air quality and community social impacts.[22–29] Psychosocial stress,[12] exposure to air pollution[4,30] including truck traffic,[31] sleep disruption,[32,33] and reduced socioeconomic status[34] are all biologically plausible pathways for UNGD to affect asthma exacerbations. To date, there have been no epidemiologic studies of UNGD and objective respiratory outcomes. Respiratory outcomes are appropriate outcomes to assess potential health impacts of UNGD because these have clear links to air pollution and stress; have short latency between exposure and health effects; are common in the general population; and prompt patients to seek care so are captured by health system data. Using electronic health record (EHR) data from the Geisinger Clinic, located in over 35 counties in Pennsylvania, including many with active UNGD, we conducted a nested case-control study of the association between four UNGD activity metrics and asthma exacerbations.

METHODS

Study Population

We identified asthma patients from the Geisinger Clinic population, which is representative of the general population in the region.[35] We included Pennsylvania and New York patients and excluded patients with cystic fibrosis (277.0x); chronic pulmonary heart disease (416.x); paralysis of vocal cords or larynx (478.3x); bronchiectasis (494.xx); and pneumoconiosis (500.xx-508.xx) using *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9*) codes. We required patients to have at least two encounters or medication orders with *ICD-9* codes for asthma on different days.[36] Patients were geocoded using previously published methods,[37] 88.9% to home address, 2.6% to ZIP+4, and 8.5% to ZIP code centroid. Inclusion criteria also included contact with Geisinger from 2005–2012 while between the ages 5–90 years and recorded information on sex (n=35,508). The study was approved by the Geisinger Institutional Review Board (with an IRB authorization agreement with Johns Hopkins Bloomberg School of Public Health). Patients did not receive a stipend and informed consent was obtained through a waiver of HIPAA authorization.

Outcome Ascertainment

We identified new oral corticosteroid (OCS) medication orders, asthma emergency department encounters, and asthma hospitalizations, termed mild, moderate, and severe exacerbations, respectively. For patients with more than one exacerbation of a given type

within a calendar year, we randomly selected one event. For mild exacerbations, we distinguished new OCS medication orders from 2008–2012 for an asthma exacerbation from standing orders or OCS ordered for other diseases (Figure 1). The medication order date was considered the index date. OCS orders from before 2008 were excluded because these were not consistently captured before then. For moderate and severe exacerbations, we identified all emergency and hospitalization encounters from 2005–12. Primary or secondary diagnoses were for asthma (493.x) were used to identify emergency or hospitalization encounters. Patients who had multiple emergency or hospitalization encounters within 72 hours were considered to have a single event. Emergency and hospitalizations encounters within 72 hours were identified as a single hospitalization. The first encounter or admission date of each group of combined encounters was the index date. For patients with more than one type of exacerbation within a week, we retained only the higher category.

Controls and Matching

We identified controls from asthma patients under observation by the health system, so that if the patient were to have an exacerbation, it would be captured by the EHR. All patient contact dates were identified (e.g., encounter, order, test). Because many of the covariates and the UNGD metrics were time-varying, we needed a single date on which to assign these variables. Therefore, for controls, we randomly selected one contact date per year per patient. A case was always eligible to be a control for a less severe event; or for an event of equal or greater severity until the year of the case's event. We frequency-matched cases to controls on age category (5–12, 13–18, 19–44, 45–61, 62–74, 75+ years), sex (male, female), and year of encounter.

Covariates

We created time-varying covariates (age, season of event, smoking status, overweight and obesity, Medical Assistance [as a measure of low family socioeconomic status], type 2 diabetes) for each index date; and non-time-varying covariates (sex and race/ethnicity) for each patient. Race/ethnicity was assessed by patient self-report, and was included because it is a well-documented confounder in studies of asthma.[2] We estimated the patients' distance to nearest major and minor road using a network from the Federal Highway Administration,[38] and used patients' geographic coordinates to assign them to a community using a mixed definition of place and calculated community socioeconomic deprivation (CSD) for these places.[37,39] In cities, communities were defined by census tracts; elsewhere, communities were defined by minor civil divisions (townships and boroughs). We estimated the peak temperature on the day before each index date using data from the nearest weather station to each patient.[40]

Well Data

Well data were obtained from: the PA DEP, for well spud (start of drilling) and production; the Pennsylvania Department of Conservation and Natural Resources, for information on well stimulation (hydraulic fracturing) and depths; and SkyTruth (Shepherdstown, WV), which used crowdsourcing of aerial photographs from the U.S. Department of Agriculture to identify the location of wellpads.[41] For each well, we had information on well pad; latitude and longitude; dates of spudding, stimulation, and production; total depth; and volume of

natural gas produced and the number of production days. We imputed missing total depths (0.4%) using conditional mean imputation. We estimated missing production quantities (0.2%) by averaging production quantities in the prior and following period. We extrapolated missing spud (2.0%) and stimulation (34.6%) dates using the well's available dates of development by requiring that the stimulation date fall in between the spud and production date and using median durations between phases from wells without any missing dates.

Activity Metric Assignment

We estimated the UNGD activity metrics using an inverse distance-squared method for pad preparation, spud, stimulation, and production phases. We compared activity metrics on the day before, three days before, the sum of three to five days before, and the sum of one to five days before the index date, and because they were highly correlated (Spearman correlation coefficients ranged from 0.96–1.00), we used only the day before the index date. For the pad preparation and spud metrics (Equation 1):

$$\text{Activity metric for patient j}=\sum_{i=1}^{n}\frac{1}{d_{ij}^2}$$

where n is the number of wells and d_{ij}^2 is the squared-distance (meters) between well i and patient j. For the stimulation metric (Equation 2):

$$\text{Activity metric for patient j}=\sum_{i=1}^{n}\frac{t_i}{d_{ij}^2}$$

where n is the number of wells, d_{ij}^2 is the squared-distance (meters) between well i and patient j, and t_i is the total well depth (meters) of well i. Total depth was used as a surrogate for truck traffic because volume of water used during stimulation[42] was highly correlated with total depth, and water is trucked to the well during stimulation. For the production metric (Equation 3):

$$\text{Activity metric for patient j}=\sum_{i=1}^{n}\frac{\nu_i}{d_{ij}^2}$$

where n is the number of wells, d_{ij}^2 is the squared-distance (meters) between well i and patient j, and v_i is the daily natural gas production volume (m^3) of well i. Production volume was used as a surrogate for fugitive emissions and compressor engine activity.[22]

Based on descriptions of the process[19] and our data, we estimated that pad development lasted 30 days before the spud date for the first well on a pad, drilling lasted between 1–30 days after the spud date based on total depth, and stimulation lasted seven days. All wells in Pennsylvania in a given phase on the day prior to an index date contributed to that phase's activity metric (Equations 1–3). We divided the four continuous metrics into quartiles using all 69,548 index dates from all three outcomes so the cutpoints were the same for all outcomes (very low, low, medium, and high).

Statistical Analysis

To assess the association of the four UNGD activity metrics with the three types of asthma exacerbations, we used multilevel logistic regression with random intercept for patient and community to account for multiple events per patient and patient clustering within communities. The base model included one of the four UNGD activity metrics (very low, low, medium, high), age category (5–12, 13–18, 19–44, 45–61, 62–74, 75+ years), sex (male, female), race/ethnicity (black, Hispanic, other, white), family history of asthma (yes, no), smoking status (former, current, missing, never), season (summer, fall, winter, spring), Medical Assistance (yes, no), and overweight/obesity (using BMI percentile for children and BMI for adults[43]) as covariates. We then added, one at a time, type 2 diabetes (yes, no), CSD (quartiles), distances to nearest major and minor arterial road (meters, z-transformed), and maximum temperature on the day prior to event (°C per interquartile range) (eFigure 1). We included the continuous covariates as linear and quadratic terms to allow for non-linearity. We used a 2-sided type 1 error rate of 0.05 for significance testing. We used Stata version 11.2 (StataCorp Inc.) and R version 3.1.2 (R Foundation for Statistical Computing).

Model Building—We calculated the intraclass correlation coefficient for the person and community levels. The proportions of total variance that were accounted for by between-community variation and between-person variation, respectively, were 14% and 63% for severe exacerbations, 41% and 89% for moderate exacerbations, and 1.2% and 59% for mild exacerbations. We evaluated covariates for conditional significance as they were added to the models.

Sensitivity Analyses—To evaluate how the four separate UNGD activity metrics compared to a summary measure, we calculated z-scores using continuous metrics, summed the z-scores, and re-ran the final models with this combined UNGD activity metric (quartiles). To explore whether an unmeasured confounder was responsible for our associations, we evaluated associations with encounters for a negative control[44] (intestinal infectious disease and noninfectious gastroenteritis, ICD-9 codes 001-009 and 558.9) among asthma patients, and we also replaced the UNGD activity metric with indicators for counties. We were concerned about the unbalanced numbers of cases and controls for certain age categories, sex, and years in the mild exacerbations analysis, so we reran the analysis dropping the unbalanced cells. In order to check the sensitivity to geocoding level, we reran the final model for the production UNGD metric and each outcome using only patients who were geocoded to their home address. We estimated how large an unmeasured confounder would need to be to account for the observed associations, in whole or in part.[45]

RESULTS

Descriptions of Wells and Patients

Between 2005–2012, 6,253 unconventional natural gas wells were spudded on 2,710 pads, 4,728 were stimulated, and 3,706 were in production. The median number of wells per pad was 1 (IQR 1–3) and median total depth was 3,394m (IQR 2,934–3,839). Most development occurred after 2007 (Figure 2). On their index date, patients in the highest group of the spud metric lived a median of 19km from the closest spudded well, compared to 63km for

patients in the lowest group. We identified 5,600 severe, 2,291 moderate, and 25,647 mild exacerbations. After retaining one event per type per year per person, 4,782 severe, 1,870 moderate, and 20,749 mild exacerbations were included. There was substantial overlap of patients and wells in the northern counties (Figure 3), and substantial overlap of patients by quartile of UNGD activity metric (eFigure 2).

Demographic and clinical variables differed by outcome (Table 1). Compared to patients with mild and moderate exacerbations, patients with severe exacerbations were more likely to be female, older, current smokers, and obese (all $p<0.001$). Patients with moderate exacerbations were more likely to be on Medical Assistance and of black race than patients with the other two outcomes, and patients with mild exacerbations were more likely to live in townships (all $p<0.001$) than patients with the other two outcomes.

Associations of UNGD Activity Metrics with Asthma Outcomes

For severe, moderate, and mild exacerbations, the average percent changes for all odds ratios, from simple models with random intercepts for person and place without covariates to fully adjusted multilevel models, were −8.5%, −0.2%, and 6.0%, respectively, suggesting little sensitivity of the associations to measured covariates. In adjusted models, the high activity (vs. very low) of each UNGD metric was associated with each asthma outcome (Table 2), except for the pad metric with mild exacerbations. Associations for the other 11 exposure-outcome pairs ranged from (odds ratio [95% confidence interval]) 1.5 (1.2–1.7) for pad metric with severe exacerbations to 4.4 (3.8–5.2) for production metric with mild exacerbations. Of the 12 activity metric-outcome pairs, six had increasing odds ratios across quartiles 2–4.

Sensitivity Analyses

The four UNGD activity metrics, calculated for all case and control index dates (n=69,548), were correlated with one another (Spearman correlation coefficients of the continuous variables ranged from 0.73–0.91). In the analysis to evaluate associations of a combined UNGD activity metric of the four phases of development, the odds ratio point estimates were between those from regressions of each phase separately. In the negative disease control analysis, we found no association of the spud activity metric with gastrointestinal illness. In a model evaluating associations of counties with outcomes (UNGD metrics removed), counties with high UNGD activity were not associated with outcomes. In the analysis that removed cells with unbalanced numbers of cases and controls in the mild exacerbation analysis, associations were attenuated (odds ratios decreased by 5%, 17%, 37%, and 55% for the high group odds ratio for the pad, spud, stimulation, and production metrics, respectively, all odds ratios $p<0.05$). In the analysis to evaluate the impact of different quality of geocoding, associations were unchanged. In the analysis of the mild and severe exacerbations, we determined that even an unmeasured confounder strongly associated with both UNGD activity and outcome (e.g., both odds ratios = 3.0), and a prevalence of 0.3 in the exposed group, would not likely change our inference about associations, given our models. However, for moderate exacerbations, an unmeasured confounder with the same characteristics could account for two of the three statistically significant associations.

DISCUSSION

We conducted a nested case-control study in a large number of asthma patients using EHR data in Pennsylvania from 2005–2012, a period of rapid development. In this first study of UNGD and objective respiratory outcomes, we found consistent associations of four UNGD activity metrics with three types of asthma exacerbations. Whether these associations are causal awaits further investigation, including more detailed exposure assessment.

Asthma is a suitable outcome because UNGD has community and environmental impacts that could affect it; it is highly prevalent; it can be exacerbated by stress and small changes in air quality with short latency; and patients usually seek care for exacerbations so they are captured by an EHR. By leveraging longitudinal EHR data, we were able to complete a number of sensitivity analyses that suggested the associations were robust to increasing levels of adjustment, although in some cases they were attenuated.

Studies of air pollution and asthma exacerbations have generally found small but consistently increased risks. A study of pediatric emergency department visits for asthma in Atlanta found that a standard deviation increase in pollution had associated risk ratios of 1.020, 1.036, and 1.062 for particulate matter < 10μm, nitrogen dioxide, and ozone, respectively.[46] Studies on psychosocial stress have found that in children with asthma, the risk of an asthma exacerbation increased 4.7 times in the two days following a very stressful event.[47] Adults exposed to violence in their community have 2.3 and 2.5 times the risk of an asthma emergency department visit and hospitalization, respectively, than those not exposed to community violence.[48]

Two sensitivity analyses were directed to the very important possibility that unmeasured confounding could account for our results. First, UNGD metrics were not associated with the negative disease control. Second, in the analysis replacing UNGD metrics with indicators for counties, counties with UNGD were not associated with severe exacerbations. These both provide evidence that unmeasured confounding is unlikely to account for our findings, but we acknowledge that the possibility still exists. We note that an unmeasured confounder would need to be strongly associated with both UNGD and asthma outcomes to account for our results. In sensitivity analysis to address unbalanced numbers of cases and controls, results were attenuated; the majority of dropped patients comprised the most susceptible groups (younger and older) in the most exposed years, so attenuation was not unexpected. Finally, geocoding method and analysis with an overall activity metric did not change inferences.

This study had several strengths, including a large sample size from a population that represents the general population in the region. Additionally, our exposure assessment improved on in prior studies,[49,50] which used categorical distance-based metrics, that did not account for UNGD phases. Our metric incorporated the temporality and duration of phases, gas production volume, and a surrogate for truck traffic. This study also improved on outcome ascertainment used in the previous study on UNGD and respiratory outcomes,[50] which relied on self-reported outcomes and grouped several respiratory symptoms and conditions together (including asthma). We used documented asthma exacerbations. Our

findings were robust to increasing levels of covariate control and in several sensitivity analyses.

This study also had limitations. The EHR does not collect information on occupation and only keeps patients' most recent address. However, comparing addresses used in a prior study[35] to addresses used in this study (39 months apart), 79.8% of patients were at the same address and an additional 7.4% and 7.6% were less than 3.2km and 3.2–16km, respectively, from their prior address, indicating little residential mobility. The EHR only collects data on events that occur at Geisinger facilities, but ambulances go to the closest hospital, so we may have under-counted events. We were unable to differentiate between asthma exacerbations that were hospitalized from those that occurred while hospitalized. We frequency-matched cases and controls for year because UNGD activity metrics and year were highly correlated. We did not include year in the final model because of this high correlation, so there remains the possibility of unmeasured residual confounding by factors that strongly vary by year. We kept all four UNGD metrics because of *a priori* evidence that exposures differed by phase, but because metrics were highly correlated we were unable to definitively distinguish among them. Furthermore, our UNGD metrics do not provide insight into the mechanism of the associations we observed.

Asthma is a common disease with large individual and societal burdens, so the possibility that UNGD may increase risk for asthma exacerbations requires public health attention. As ours is the first study of UNGD and objective respiratory outcomes, and several other health outcomes have not been investigated to date, there is an urgent need for more health studies. These should include more detailed exposure assessment to better characterize pathways and identify the phases of development that present the most risk.

Acknowledgments

Sara G. Rasmussen and Brian S. Schwartz had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Brian S. Schwartz is a Fellow of the Post Carbon Institute (PCI), serving as an informal advisor on climate, energy, and health issues. He receives no payment for this role. His research is entirely independent of PCI, and is not motivated, reviewed, or funded by PCI.

Source of Funding: This study was funded by the National Institute of Environmental Health Sciences grant ES023675-01 (PI: B S Schwartz) and training grant ES07141 (S G Rasmussen). Additional support was provided by the Degenstein Foundation for compilation of well data, the Robert Wood Johnson Foundation Health & Society Scholars program (J A Casey), and the National Science Foundation Integrative Graduate Education and Research Traineeship (S G Rasmussen). No funders had input into the study design, conduct, data collection or analysis, or manuscript preparation.

References

1. Moorman JE, Akinbami LJ, Bailey CM, Johnson CA, et al. National surveillance of asthma: United States, 2001–2010. National Center for Health Statistics, Vital Health Stat. 2012; 3:35.
2. National Heart, Lung, and Blood Institute. Expert panel report 3: Guidelines for the diagnosis and management of asthma: Full report. US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2007. National Asthma Education Program. Expert Panel on the Management of Asthma.
3. Dougherty R, Fahy JV. Acute exacerbations of asthma: Epidemiology, biology and the exacerbation-prone phenotype. Clinical & Experimental Allergy. 2009; 39(2):193–202. [PubMed: 19187331]

4. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. The Lancet. 2014; 383(9928):1581–1592.
5. Gent JF, Triche EW, Holford TR, et al. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. JAMA. 2003; 290(14):1859–1867. [PubMed: 14532314]
6. Peel JL, Tolbert PE, Klein M, et al. Ambient air pollution and respiratory emergency department visits. Epidemiology. 2005; 16(2):164–174. [PubMed: 15703530]
7. Ostro B, Lipsett M, Mann J, Braxton-Owens H, White M. Air pollution and exacerbation of asthma in African-American children in Los Angeles. Epidemiology. 2001; 12(2):200–208. [PubMed: 11246581]
8. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA. 2006; 295(10):1127–1134. [PubMed: 16522832]
9. Ko F, Tam W, Wong T, et al. Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. Clinical & Experimental Allergy. 2007; 37(9):1312–1319. [PubMed: 17845411]
10. Schildcrout JS, Sheppard L, Lumley T, Slaughter JC, Koenig JQ, Shapiro GG. Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am J Epidemiol. 2006; 164(6):505–517. [PubMed: 16798793]
11. Halonen JI, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J. Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax. 2008; 63(7):635–641. [PubMed: 18267984]
12. Yonas MA, Lange NE, Celedón JC. Psychosocial stress and asthma morbidity. Current Opinion in Allergy and Clinical Immunology. 2012; 12(2):202–210. [PubMed: 22266773]
13. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun. 2007; 21(8):993–999. [PubMed: 17493786]
14. Wisnivesky JP, Lorenzo J, Feldman JM, Leventhal H, Halm EA. The relationship between perceived stress and morbidity among adult inner-city asthmatics. Journal of Asthma. 2010; 47(1): 100–104. [PubMed: 20100028]
15. New York State Department of Health Completes Review of High-volume Hydraulic Fracturing [press release]. Albany, NY: New York State Department of Enviornmental Conservation; Dec 17. 2014
16. Cox E. Assembly votes to ban fracking for two years. Baltimore Sun. Apr 10.2015
17. Werner AK, Vink S, Watt K, Jagals P. Environmental health impacts of unconventional natural gas development: A review of the current strength of evidence. Sci Total Environ. 2015; 505:1127–1141. [PubMed: 25461113]
18. Mitka M. Rigorous evidence slim for determining health risks from natural gas fracking. JAMA. 2012; 307(20)
19. Gaines, M. PennDOT's posting and bonding program and impact of unconventional oil & gas [webinar]. http://extension.psu.edu/natural-resources/natural-gas/webinars/shale-energy-developments-effect-on-the-posting-bonding-and-maintenance-of-roads-in-rural-pa/mark-gaines-may-16-2013-powerpoint. Published May 16, 2013
20. Maloney KO, Yoxtheimer DA. Production and disposal of waste materials from gas and oil extraction from the Marcellus shale play in Pennsylvania. Env Prac. 2012; 14(04):278–287.
21. Pennsylvania Code. Subchapter E. Well reporting § 78.121–§78.125. http://www.pacode.com/secure/data/025/chapter78/subchapEtoc.html
22. Roy AA, Adams PJ, Robinson AL. Air pollutant emissions from the development, production, and processing of Marcellus shale natural gas. J Air Waste Manage Assoc. 2013; 64(1):19–37.
23. Litovitz A, Curtright A, Abramzon S, Burger N, Samaras C. Estimation of regional air-quality damages from Marcellus shale natural gas extraction in Pennsylvania. Environmental Research Letters. 2013; 8(1):014017.
24. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ. 2012; 424:79–87. [PubMed: 22444058]

25. Sangaramoorthy T, Jamison AM, Boyle MD, et al. Place-based perceptions of the impacts of fracking along the Marcellus shale. Soc Sci Med. 2016
26. Adgate JL, Goldstein BD, McKenzie LM. Potential public health hazards, exposures and health effects from unconventional natural gas development. Environ Sci Technol. 2014; 48(15):8307–8320. [PubMed: 24564405]
27. Vinciguerra T, Yao S, Dadzie J, et al. Regional air quality impacts of hydraulic fracturing and shale natural gas activity: Evidence from ambient VOC observations. Atmos Environ. 2015; 110:144–150.
28. Gopalakrishnan S, Klaiber HA. Is the shale energy boom a bust for nearby residents? evidence from housing values in Pennsylvania. Am J Agric Econ. 2014; 96(1):43–66.
29. Muehlenbachs L, Spiller E, Timmins C. The housing market impacts of shale gas development. Am Econ Rev. 2015; 105(12):3633–59.
30. Brunekreef B, Holgate ST. Air pollution and health. Lancet. 2002; 360:1233–1242. [PubMed: 12401268]
31. Salam MT, Islam T, Gilliland FD. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. Curr Opin Pulm Med. 2008; 14(1):3–8. [PubMed: 18043269]
32. Hanson MD, Chen E. Brief report: The temporal relationships between sleep, cortisol, and lung functioning in youth with asthma. J Pediatr Psychol. 2007; 33(3):312–316. [PubMed: 18056138]
33. Daniel LC, Boergers J, Kopel SJ, Koinis-Mitchell D. Missed sleep and asthma morbidity in urban children. Annals of Allergy, Asthma & Immunology. 2012; 109(1):41–46.
34. Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA. Asthma exacerbations in North American adults: Who are the “frequent fliers” in the emergency department? Chest Journal. 2005; 127(5):1579–1586.
35. Casey JA, Cosgrove SE, Stewart WF, Pollak J, Schwartz BS. A population-based study of the epidemiology and clinical features of methicillin-resistant staphylococcus aureus infection in Pennsylvania, 2001–2010. Epidemiol Infect. 2013; 141(06):1166–1179. [PubMed: 22929058]
36. Pacheco JA, Avila PC, Thompson JA, et al. A highly specific algorithm for identifying asthma cases and controls for genome-wide association studies. AMIA Annu Symp Proc. 2009; 2009:497–501. [PubMed: 20351906]
37. Schwartz BS, Stewart WF, Godby S, et al. Body mass index and the built and social environments in children and adolescents using electronic health records. Am J Prev Med. 2011; 41(4):e17–e28. [PubMed: 21961475]
38. U.S. Department of Transportation Federal Highway Administration. Highway Performance Monitoring System website. http://www.fhwa.dot.gov/policyinformation/hpms/shapefiles.cfm. Updated 2013. Accessed March 27, 2015
39. Liu AY, Curriero FC, Glass TA, Stewart WF, Schwartz BS. The contextual influence of coal abandoned mine lands in communities and type 2 diabetes in Pennsylvania. Health Place. 2013
40. National Climatic Data Center. Climate Data Online website. http://www.ncdc.noaa.gov/cdo-web/. Accessed May 11, 2011
41. SkyTruth. TADPOLE Pennsylvania results. http://frack.skytruth.org/frackfinder/frackfinder-news/tadpolepennsylvaniaresults. Published Feb 12, 2014. Updated 2014. Accessed June 30, 2014
42. SkyTruth. Fracking chemical database. http://frack.skytruth.org/fracking-chemical-database. Updated 2013. Accessed November 27, 2013
43. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the united states, 2011–2012. JAMA. 2014; 311(8):806. [PubMed: 24570244]
44. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: A tool for detecting confounding and bias in observational studies. Epidemiology. 2010; 21(3):383–388. [PubMed: 20335814]
45. VanderWeele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. Epidemiology. 2011; 22(1):42–52. [PubMed: 21052008]
46. Strickland MJ, Darrow LA, Klein M, et al. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. American journal of respiratory and critical care medicine. 2010; 182(3):307–316. [PubMed: 20378732]

47. Sandberg S, Jarvenpaa S, Penttinen A, Paton JY, McCann DC. Asthma exacerbations in children immediately following stressful life events: A cox's hierarchical regression. Thorax. 2004; 59(12): 1046–1051. [PubMed: 15563703]

48. Apter AJ, Garcia LA, Boyd RC, Wang X, Bogen DK, Ten Have T. Exposure to community violence is associated with asthma hospitalizations and emergency department visits. J Allergy Clin Immunol. 2010; 126(3):552–557. [PubMed: 20816190]

49. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect. 2014

50. Rabinowitz PM, Slizovskiy IB, Lamers V, et al. Proximity to natural gas wells and reported health status: Results of a household survey in Washington County, Pennsylvania. Environ Health Perspect. 2014

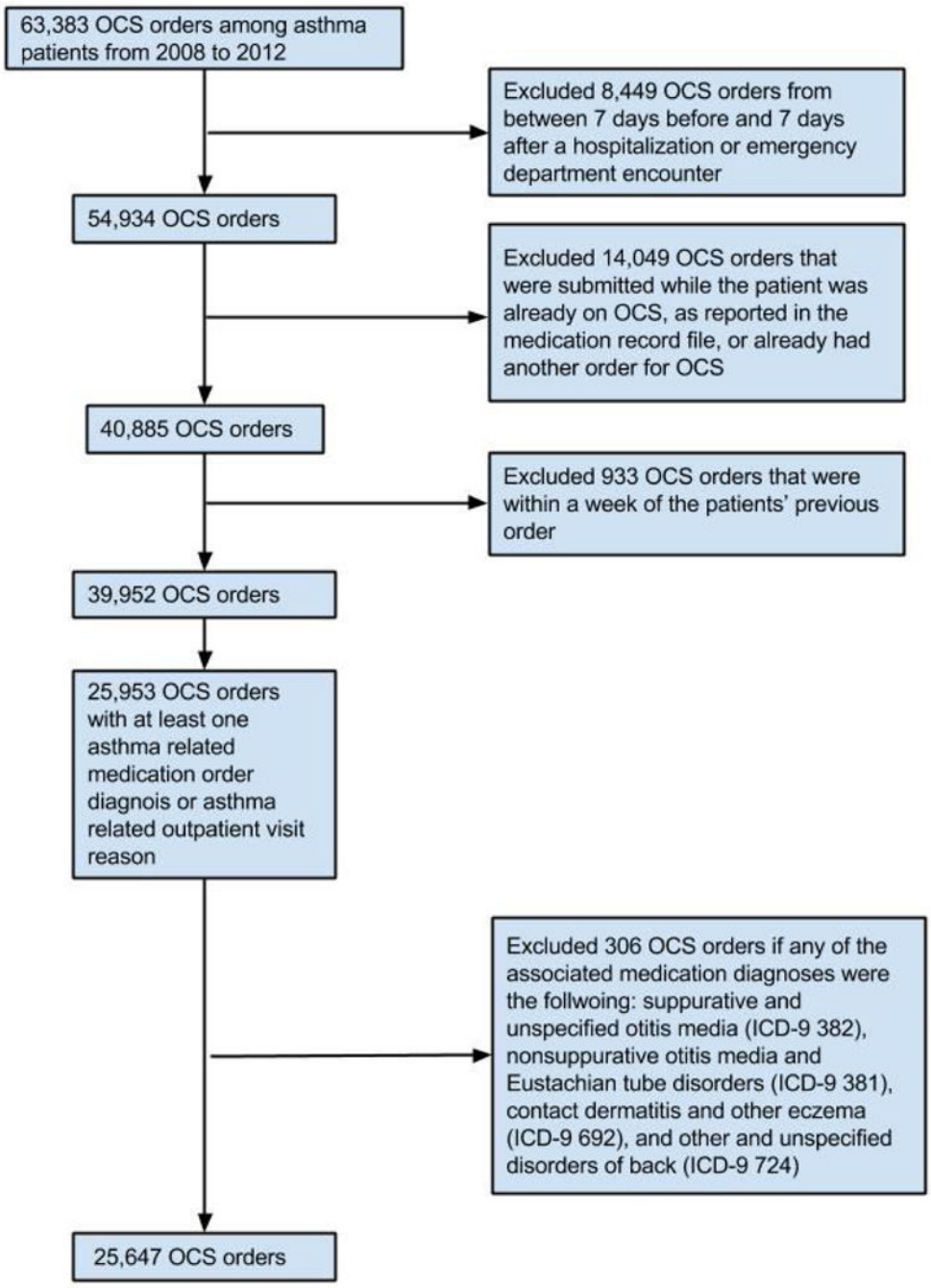


Figure 1.
Flow diagram for identification of new asthma oral corticosteroid (OCS) medication orders.

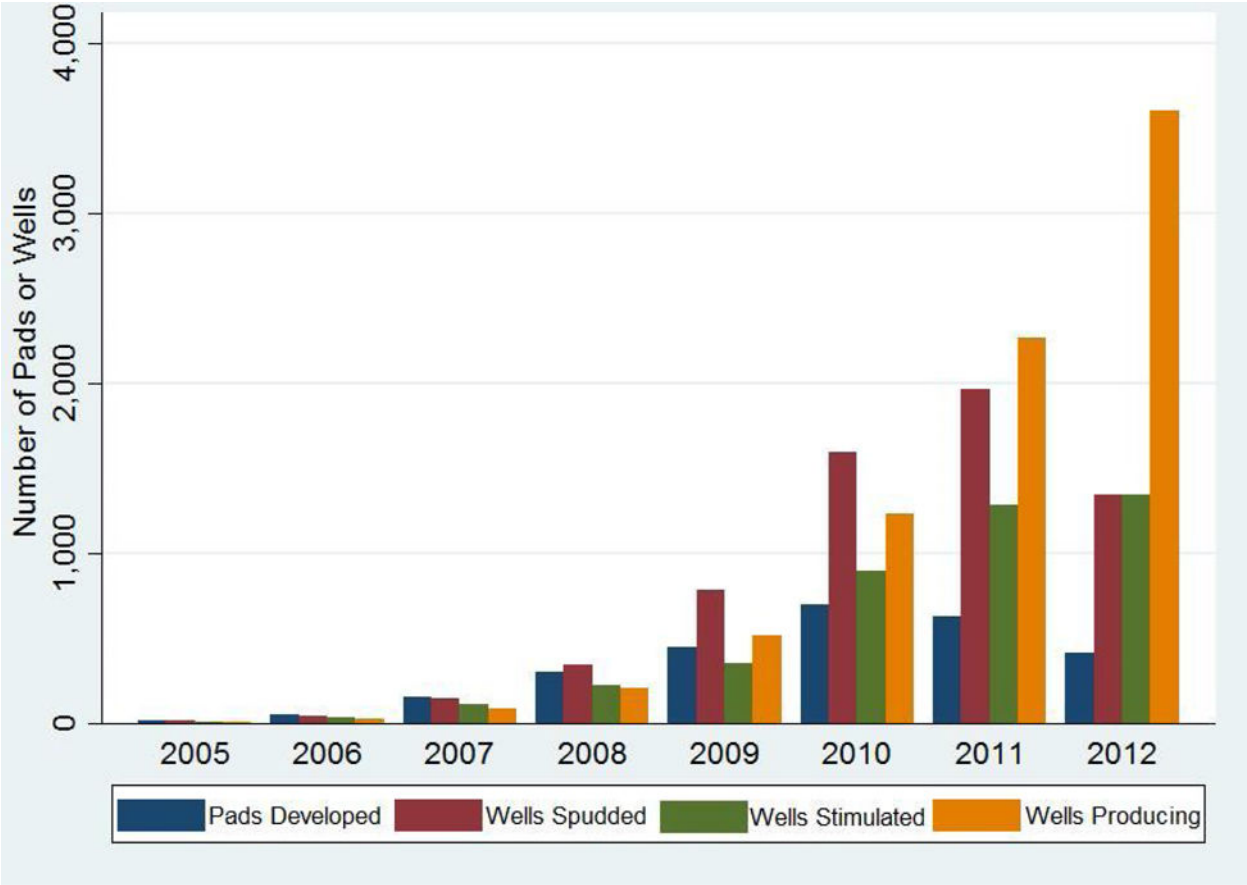
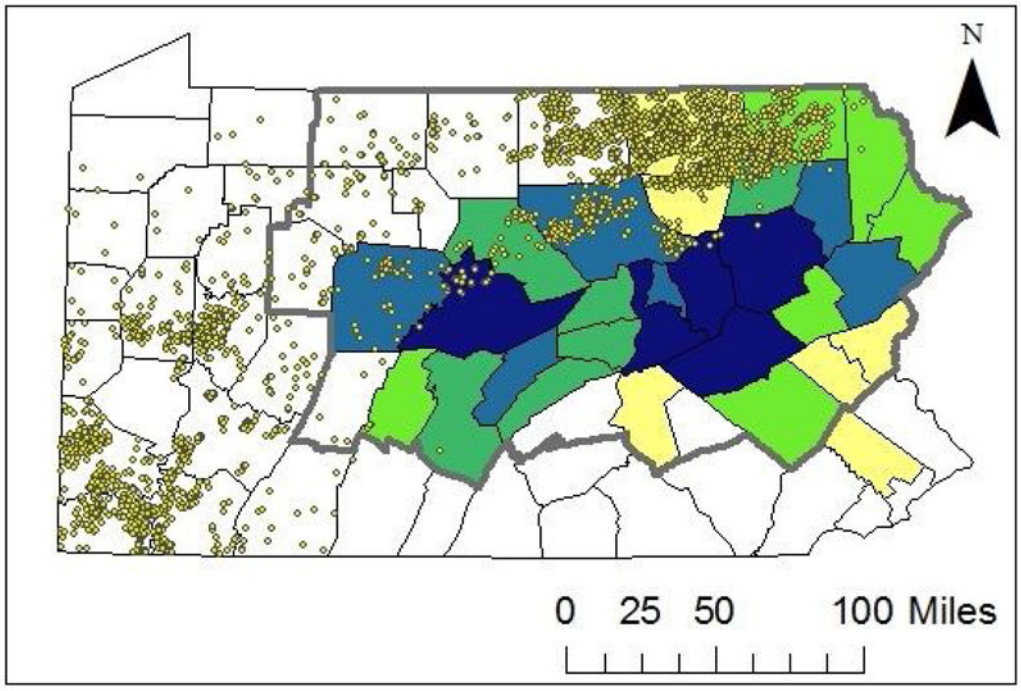


Figure 2.
Number of developed pads (blue), and spudded (red), stimulated (green), and producing wells (yellow), 2005–12.



Legend

- Spudded wells
- Geisinger primary catchment area

Number of asthma patients per county[a], quintiles

- 21 - 63
- 64 - 335
- 336 - 964
- 965 - 1955
- 1956 - 5734
- Counties with less than 20 patients

[a]Asthma patients in New York (n = 72) not shown.

Figure 3.
The location of spudded wells as of December 2012 and residential location of Geisinger asthma patients.

JAMA Intern Med. Author manuscript; available in PMC 2017 May 10.

Table 1

Descriptive statistics of cases and controls by exacerbation type for selected study variables by variable type (constant vs. time-varying)

	Hospitalization		Emergency Department Encounter		Oral Corticosteroid Order	
	Control n (%[a])	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)
Non-time-varying (constant) variables						
Total number of patients	14104 (100)	3576 (100)	9350 (100)	1454 (100)	18693 (100)	13196 (100)
Female	10093 (71.6)	2520 (70.5)	5660 (60.5)	872 (60)	11297 (60.4)	8173 (61.9)
Family history of asthma	1324 (9.4)	404 (11.3)	1147 (12.3)	266 (18.3)	2047 (11)	1672 (12.7)
Race/ethnicity						
White	13309 (94.4)	3316 (92.7)	8705 (93.1)	1223 (84.1)	17160 (91.8)	12177 (92.3)
Black	345 (2.4)	111 (3.1)	286 (3.1)	125 (8.6)	676 (3.6)	431 (3.3)
Hispanic	344 (2.4)	126 (3.5)	273 (2.9)	93 (6.4)	674 (3.6)	471 (3.6)
Other/missing	106 (0.8)	23 (0.6)	86 (0.9)	13 (0.9)	183 (1.0)	117 (0.9)
Place type						
Township	8583 (60.9)	2017 (56.4)	5590 (59.8)	659 (45.3)	11324 (60.6)	7917 (60)
Borough	4192 (29.7)	1108 (31)	2786 (29.8)	490 (33.7)	5445 (29.1)	3891 (29.5)
City	1329 (9.4)	451 (12.6)	974 (10.4)	305 (21)	1924 (10.3)	1388 (10.5)
Community socioeconomic deprivation						
Quartile 1	2967 (21)	673 (18.8)	1936 (20.7)	226 (15.5)	3897 (20.8)	2751 (20.8)
Quartile 2	3677 (26.1)	886 (24.8)	2454 (26.2)	307 (21.1)	4839 (25.9)	3259 (24.7)
Quartile 3	3561 (25.2)	920 (25.7)	2294 (24.5)	378 (26.0)	4659 (24.9)	3427 (26.0)
Quartile 4	3899 (27.6)	1097 (30.7)	2666 (28.5)	543 (37.3)	5298 (28.3)	3759 (28.5)
Total number of events[b]						
0	14104 (100)	0 (0)	9350 (100)	0	18693 (100)	0 (0)
1	0 (0)	2732 (76.4)	0 (0)	1169 (80.4)	0 (0)	8205 (62.2)
2	0 (0)	605 (16.9)	0 (0)	208 (14.3)	0 (0)	3138 (23.8)
3	0 (0)	162 (4.5)	0 (0)	46 (3.2)	0 (0)	1273 (9.6)
4	0 (0)	48 (1.3)	0 (0)	20 (1.4)	0 (0)	451 (3.4)
5	0 (0)	20 (0.6)	0 (0)	5 (0.3)	0 (0)	129 (1)

	Hospitalization		Emergency Department Encounter		Oral Corticosteroid Order	
	Control n (%[a])	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)
6	0 (0)	3 (0.1)	0 (0)	3 (0.2)	0 (0)	0 (0)
7	0 (0)	4 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
8	0 (0)	2 (0.1)	0 (0)	3 (0.2)	0 (0)	0 (0)
Time-varying variables						
Encounters (controls) or events (cases)[c]	14104 (100)	4782 (100)	9350 (100)	1870 (100)	18693 (100)	20749 (100)
Age (years) at event or matched encounter						
5 to < 13	1062 (7.5)	354 (7.4)	2265 (24.2)	453 (24.2)	4157 (22.2)	4245 (20.5)
13 to < 19	810 (5.7)	269 (5.6)	995 (10.6)	199 (10.6)	1926 (10.3)	1926 (9.3)
19 to < 45	5253 (37.2)	1751 (36.6)	4105 (43.9)	821 (43.9)	6013 (32.2)	6323 (30.5)
45 to < 62	4014 (28.5)	1338 (28)	1390 (14.9)	278 (14.9)	4313 (23.1)	5353 (25.8)
62 to < 75	1983 (14.1)	661 (13.8)	405 (4.3)	81 (4.3)	1613 (8.6)	2113 (10.2)
> 75 years	982 (7.0)	409 (8.6)	190 (2.0)	38 (2.0)	671 (3.6)	789 (3.8)
Year of encounter						
2005	1593 (11.3)	531 (11.1)	845 (9)	169 (9)	0 (0)	0 (0)
2006	1767 (12.5)	589 (12.3)	905 (9.7)	181 (9.7)	0 (0)	0 (0)
2007	1659 (11.8)	552 (11.5)	1185 (12.7)	237 (12.7)	0 (0)	0 (0)
2008	1563 (11.1)	526 (11)	1220 (13)	244 (13)	3375 (18.1)	3375 (16.3)
2009	1819 (12.9)	608 (12.7)	1380 (14.8)	276 (14.8)	4038 (21.6)	4038 (19.5)
2010	1794 (12.7)	603 (12.6)	1205 (12.9)	241 (12.9)	4019 (21.5)	4019 (19.4)
2011	1886 (13.4)	648 (13.6)	1230 (13.2)	246 (13.2)	4286 (22.9)	4624 (22.3)
2012	2023 (14.3)	725 (15.2)	1380 (14.8)	276 (14.8)	2975 (15.9)	4693 (22.6)
Season of encounter[d]						
Spring	3447 (24.4)	1219 (25.5)	2218 (23.7)	456 (24.4)	4337 (23.2)	4618 (22.3)
Summer	3357 (23.8)	1134 (23.7)	2253 (24.1)	380 (20.3)	4536 (24.3)	3207 (15.5)
Fall	4171 (29.6)	1183 (24.7)	2724 (29.1)	553 (29.6)	5695 (30.5)	6995 (33.7)
Winter	3129 (22.2)	1246 (26.1)	2155 (23)	481 (25.7)	4125 (22.1)	5929 (28.6)
Obesity[e]						
Not overweight/obese	3728 (26.4)	1046 (21.9)	3366 (36)	569 (30.4)	6591 (35.3)	5737 (27.6)

	Hospitalization		Emergency Department Encounter		Oral Corticosteroid Order	
	Control n (%[a])	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)
Overweight	3605 (25.6)	1077 (22.5)	2173 (23.2)	376 (20.1)	4441 (23.8)	4821 (23.2)
Obese	6683 (47.4)	2641 (55.2)	3762 (40.2)	895 (47.9)	7577 (40.5)	10137 (48.9)
Missing	88 (0.6)	18 (0.4)	49 (0.5)	30 (1.6)	84 (0.4)	54 (0.3)
Smoking status						
Never	7454 (52.9)	2014 (42.1)	5335 (57.1)	826 (44.2)	11375 (60.9)	11556 (55.7)
Current	2552 (18.1)	1204 (25.2)	1466 (15.7)	387 (20.7)	2589 (13.9)	3672 (17.7)
Former	3204 (22.7)	1238 (25.9)	1395 (14.9)	304 (16.3)	3231 (17.3)	4251 (20.5)
Missing	894 (6.3)	326 (6.8)	1154 (12.3)	353 (18.9)	1498 (8)	1270 (6.1)
Medical Assistance[f]	2657 (18.8)	1568 (32.8)	2529 (27)	741 (39.6)	4956 (26.5)	5850 (28.2)
Type 2 diabetes	1504 (10.7)	917 (19.2)	517 (5.5)	156 (8.3)	1420 (7.6)	1905 (9.2)
On inhaled corticosteroids	4061 (28.8)	1577 (33)	2545 (27.2)	713 (38.1)	5319 (28.5)	10458 (50.4)
Distance to nearest major road[g], median, meters	1042	826	1077.5	651.5	1064	1032
Distance to nearest minor road[h], median, meters	708.5	535	682	411	687	691
Temperature on the prior day, median, degrees Celsius	16.1	16.7	16.7	15	16.1	13.3
Pad activity metric, $10^{10}/m^2$						
Very low, less than 10.7	5988 (42.5)	2004 (41.9)	3671 (39.3)	719 (38.4)	2344 (12.5)	2661 (12.8)
Low, 10.7 to 25.7	2811 (19.9)	816 (17.1)	2096 (22.4)	350 (18.7)	5281 (28.3)	6033 (29.1)
Medium, 25.8 to 48.7	2675 (19)	887 (18.5)	1819 (19.5)	363 (19.4)	5489 (29.4)	6154 (29.7)
High, greater than 48.7	2630 (18.6)	1075 (22.5)	1764 (18.9)	438 (23.4)	5579 (29.8)	5901 (28.4)
Spud activity metric, $10^{10}/m^2$						
Very low, less than 5.1	6009 (42.6)	2032 (42.5)	3701 (39.6)	742 (39.7)	2352 (12.6)	2551 (12.3)
Low, 5.1 to 32.3	2796 (19.8)	819 (17.1)	2030 (21.7)	371 (19.8)	5491 (29.4)	5880 (28.3)
Medium, 32.4 to 66.8	2719 (19.3)	821 (17.2)	1832 (19.6)	317 (17)	5389 (28.8)	6309 (30.4)
High, greater than 66.8	2580 (18.3)	1110 (23.2)	1787 (19.1)	440 (23.5)	5461 (29.2)	6009 (29)
Stimulation activity metric, $10^{13} \times m/m^2$						
Very low, less than 2.7	5829 (41.3)	1986 (41.5)	3598 (38.5)	729 (39)	2577 (13.8)	2668 (12.9)
Low, 8,2.7 to 25.5	2876 (20.4)	858 (17.9)	2089 (22.3)	391 (20.9)	5573 (29.8)	5600 (27)

JAMA Intern Med. Author manuscript; available in PMC 2017 May 10.

	Hospitalization		Emergency Department Encounter		Oral Corticosteroid Order	
	Control n (%[a])	Case n (%)	Control n (%)	Case n (%)	Control n (%)	Case n (%)
Medium, 25.6 to 67.4	2736 (19.4)	841 (17.6)	1835 (19.6)	310 (16.6)	5415 (29)	6250 (30.1)
High, greater than 67.4	2663 (18.9)	1097 (22.9)	1828 (19.6)	440 (23.5)	5128 (27.4)	6231 (30)
Production activity metric, $10^{15} \times m^3/m^2$						
Very low, less than 2.3	6079 (43.1)	2087 (43.6)	3776 (40.4)	765 (40.9)	2345 (12.5)	2335 (11.3)
Low, 2.3 to 133.2	2629 (18.6)	794 (16.6)	1953 (20.9)	363 (19.4)	5713 (30.6)	5935 (28.6)
Medium, 133.3 to 759.7	2636 (18.7)	798 (16.7)	1789 (19.1)	271 (14.5)	5787 (31)	6106 (29.4)
High, greater than 759.7	2760 (19.6)	1103 (23.1)	1832 (19.6)	471 (25.2)	4848 (25.9)	6373 (30.7)

[a] Percentages may not add to 100 due to rounding.

[b] Cases contribute up to one event per year (events are randomly chosen from patients with multiple events in a year). Controls cannot have had a event up to the year of the hospitalization in the frequency-matched case, but can serve as a case later.

[c] For controls, the encounter is a randomly selected encounter during the year of the matched case's hospitalization and before the year of any subsequent asthma hospitalization in the control. For cases, the event is an asthma hospitalization.

[d] Spring, March 22–June 21; summer, June 22–September 21; fall, September 22–December 21; winter, December 22–March 21.

[e] For children and adults, respectively: normal, body mass index [BMI] < 85th percentile or BMI < 25 kg/m^2; overweight, BMI = 85th–<95th percentile or BMI = 25–<30 kg/m^2; obese, BMI ≥ 95th percentile or BMI ≥ 30 kg/m^2

[f] A means tested program that is a surrogate for family SES.

[g] Principal arterial or interstate

[h] Minor arterial road

Table 2

Associations of unconventional natural gas activity metrics and asthma outcomes

		Asthma Hospitalizations[a]	Asthma Emergency Department Visits[a]	OCS Orders[a]
		Odds Ratio (95% CI[b])	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Pad Activity Metric	Low[c]	1.26 (1.06 – 1.50)	1.53 (1.06 – 2.23)	1.54 (1.37 – 1.74)
	Medium	1.37 (1.15 – 1.64)	1.77 (1.2 – 2.6)	1.66 (1.47 – 1.87)
	High	1.45 (1.21 – 1.73)	1.37 (0.94 – 1.99)	1.59 (1.41 – 1.81)
Spud Activity Metric	Low	1.16 (0.98 – 1.37)	1.53 (1.06 – 2.21)	1.45 (1.29 – 1.63)
	Medium	1.26 (1.05 – 1.50)	1.54 (1.04 – 2.27)	1.98 (1.75 – 2.24)
	High	1.64 (1.38 – 1.97)	1.57 (1.08 – 2.29)	1.99 (1.75 – 2.26)
Stimulation Activity Metric	Low	1.13 (0.96 – 1.33)	1.51 (1.05 – 2.19)	1.23 (1.09 – 1.39)
	Medium	1.31 (1.10 – 1.57)	1.74 (1.17 – 2.61)	2.22 (1.95 – 2.53)
	High	1.66 (1.38 – 1.98)	1.71 (1.16 – 2.52)	3.00 (2.60 – 3.45)
Production Activity Metric	Low	1.10 (0.92 – 1.30)	1.47 (1.01 – 2.14)	1.28 (1.13 – 1.46)
	Medium	1.16 (0.97 – 1.38)	1.10 (0.74 – 1.65)	2.15 (1.87 – 2.47)
	High	1.74 (1.45 – 2.09)	2.19 (1.47 – 3.25)	4.43 (3.75 – 5.22)

[a] Multilevel models with a random intercept for patient and community, adjusted for age category (5–12, 13–18, 19–44, 45–61, 62–74, 75+ years), sex (male, female), race/ethnicity (white, black, Hispanic, other), family history of asthma (yes vs. no), smoking status (never, former, current, missing), season (spring, March 22–June 21; summer, June 22–September 21; fall, September 22–December 21; winter, December 22–March 21), Medical Assistance (yes vs. no), overweight/obesity (normal, body mass index [BMI] < 85th percentile or BMI < 25 kg/m^2; overweight, BMI = 85th–<95th percentile or BMI = 25–<30 kg/m^2; obese, BMI ≥ 95th percentile or BMI ≥ 30 kg/m^2, for children and adults, respectively; BMI missing), type 2 diabetes (yes vs. no), community socioeconomic deprivation (quartiles), distance to nearest major and minor arterial road (truncated at the 98th percentile, meters, z-transformed), squared distance to nearest major and minor arterial road (truncated at the 98th percentile, meters, z-transformed), maximum temperature on the day prior to event (degrees Celsius), and squared maximum temperature on the day prior to event (degrees Celsius)

[b] Confidence interval

[c] Very low is the reference group

SUPPLEMENT ARTICLE

Sleepless in America: Inadequate Sleep and Relationships to Health and Well-being of Our Nation's Children

Arlene Smaldone, DNSc, CPNP, CDE, Judy C. Honig, DrNP, RN, EdD, CPNP, Mary W. Byrne, PhD, MPH, FAAN

Columbia University School of Nursing, New York, New York

The authors have indicated they have no financial interests relevant to this study to disclose.

ABSTRACT

OBJECTIVE. Our goal was to identify characteristics associated with inadequate sleep for a national random sample of elementary school–aged children (6–11 years) and adolescents (12–17 years).

METHODS. Data from 68 418 participants in the 2003 National Survey of Children's Health were analyzed by using weighted bivariate and multivariate regression models. The dependent variable was report of not getting enough sleep for a child of his or her age ≥1 night of the past week. Independent variables included demographic characteristics, child health, school and other activities, and family life.

RESULTS. Parents of elementary school–aged children with inadequate sleep were more likely to report that their child was having problems at school or had a father with fair or poor health. Parents of adolescents with inadequate sleep were more likely to report that their child had an atopic condition, frequent or severe headaches, a parent with less-than-excellent emotional health, or experienced frequent parental anger. Inadequate sleep in both age groups was associated with parental report that their child usually or always displayed depressive symptomatology, family disagreements involved heated arguing, or parental concern that the child was not always safe at home, at school, or in their neighborhood.

CONCLUSIONS. Approximately 15 million American children are affected by inadequate sleep. Primary care providers should routinely identify and address inadequate sleep and its associated health, school, and family factors.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-2089F

doi:10.1542/peds.2006-2089F

Key Words
sleep, child health, national estimates, school age, teens

Abbreviations
ADHD—attention-deficit/hyperactivity disorder
NSCH—National Survey of Children's Health
ADD—attention-deficit disorder
PL—poverty level
OR— odds ratio
CI— confidence interval

Accepted for publication Sep 15, 2006

Address correspondence to Arlene Smaldone, DNSc, CPNP, CDE, Columbia University School of Nursing, 630 W 168th St, New York, NY 10032. E-mail: ams130@columbia.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275); published in the public domain by the American Academy of Pediatrics

INADEQUATE SLEEP DURING childhood is an invisible phenomenon that fails to receive attention from primary care providers until it interferes with the child's behavior, mood, or performance.[1–4] Community and multi-site studies have consistently reported that up to 20% to 25% of US children and adolescents experience a range of sleep problems.[5–10] Inadequate sleep takes many forms: difficulty with sleep onset, length, or circadian rhythms with resulting daytime sleepiness experienced by otherwise healthy children; disturbed sleep associated with acute and chronic illness; and primary sleep disorders. The least attention has been paid to the first group, and there is little consensus about the second.

Normative requirements for adequate sleep based on epidemiologic and laboratory studies[11–13] reflect the need for progressively less sleep by developmental stage with averages of 10 hours for 5- to 13-year-olds (declining from 11.1 at 5 years to 9.0 hours at 13 years) and 8 to 9 hours for adolescents 14 to 18 years of age.[11] More recent reports suggest that adolescent needs may be underestimated,[6] especially during midadolescence.[14] Evidence is accumulating that US children and teens typically sleep less than the required hours recommended.[8–10,15,16] Primary care providers inadequately assess, diagnose, or treat sleep problems even when parents and children offer complaints.[1] Strength of associations between sleep disturbances and cognition, behavior, or mood in otherwise healthy children range from robust to unknown.[17]

Relationships between sleep disturbance and chronic health conditions during childhood have been investigated. The association of sleep and attention-deficit/hyperactivity disorder (ADHD) is not well understood. The consequences of impaired sleep may resemble and/or exacerbate ADHD symptomatology. Conversely, ADHD symptoms and psychostimulant medication may exacerbate sleep impairment. Although as many as 50% of parents of children and adolescents with ADHD report sleep problems,[18–20] studies using more objective polysomnography have failed to demonstrate differences in sleep architecture between children with and without ADHD.[20]

Similarly, both research and clinical experience supports the relationship between sleep problems and mood and anxiety disorders, although it is unclear whether the sleep problem or the psychiatric disorder is the primary problem.[21,22] In some studies, primary psychopathology is associated with or worsened by sleep impairment.[7] Consistently, sleep impairment and mood and anxiety disorders are comorbid conditions. Atopic disorders, such as asthma and allergic rhinitis, have also been associated with increased sleep impairment.[2,23,24]

The purpose of this study was to describe the prevalence and characteristics of inadequate sleep as perceived by parents of a random national sample of school-aged and adolescent children and reported as part of the 2003 National Survey of Children's Health (NSCH). We use a multi-domain conceptual approach incorporating child, family, and environmental factors. The assumptions are made that children require regular patterns and specific hours of sleep according to developmental stage and that inadequate sleep is undesirable and potentially deleterious to health.

METHODS

Data Source

Data for this study come from the responses of parents or caregivers of 68 418 children between the ages of 6 and 17 years interviewed as part of the 2003 NSCH who responded to the question "During the past week, on how many nights did your child get enough sleep for a child his/her age?" "Enough sleep" was broadly interpreted as however the parent/caregiver defined it for a particular child. Parents of children <6 years of age were not asked this question as part of the survey. The survey design is described briefly in the article by Kogan and Newacheck[25] in this issue; more in-depth information can be found elsewhere.[26]

Variables

We stratified children by age into 2 groups: school-aged children (6–11 years) and adolescents (12–17 years). Independent variables were organized by the following categories: demographic characteristics, child health (health status, comorbid conditions, and reported child behaviors); school and activities (problems in school, physical activity, and television viewing), and family/community life (family structure, parental health, and family stress). The dependent variable, inadequate sleep, was a response to the question on the survey indicating that the child did not sleep well on at least 1 night of the preceding week.

Some variables and/or response categories were merged into broader categories before inclusion in bivariate or multivariate models. Race and ethnicity variables were merged to encompass non-Hispanic white, non-Hispanic black, Hispanic, and other race. The category "other race" was inclusive of children identified as Asian or Native American. We dichotomized responses to questions about time spent watching television, watching videos, or playing video games at ≥2 hours and <2 hours in accord with the guidelines established by the American Academy of Pediatrics.[27] We merged responses to 3 questions that asked parents whether a doctor or other health professional had told them that their child had asthma, hay fever or another respiratory allergy, or eczema or another skin allergy to create the variable "atopic condition."

A variable "depressive symptoms" was created from collective responses to 4 questions that asked about level of parental concern regarding the following child behav-

ioral characteristics: stubborn, sullen, or irritable; feeling worthless or inferior; unhappy, sad, or depressed; and withdrawn and does not get involved with others. We quantified level of concern for depressive symptoms as "never concerned," indicating that the respondent did not express concern about any of the 4 component variables, and "sometimes" or "usually/always" concerned if the respondent expressed this level of concern for at least 1 of the 4 behaviors. We used a similar approach to create the variable "environmental safety" from 3 questions that asked parents how often they felt their child was safe in their community or neighborhood, school, and home. Human subjects review was not required for this study.

Analyses

The NSCH provides population weights to permit extrapolation of findings from this sample to national and state population estimates. Incorporating the appropriate weights, we used SUDAAN 9.0.0 (Research Triangle Institute, Research Triangle, NC)[28] to perform all of our analyses. Bivariate analyses were conducted to examine relationships between the outcome variable, inadequate sleep, and variables included in each of the categories specified above for children 6 to 11 years of age and 12 to 17 years of age who experienced inadequate sleep with those who did not. Multivariate logistic regression analyses were performed to assess the independent associations between inadequate sleep and covariates of interest for each group of children.

RESULTS

The 68 418 children identified for interviews were weighted to represent 47.4 million children nationwide. Overall, the parents of 31.9% of these children reported that their child's sleep had been inadequate on ≥1 night during the week before participation in the survey. The percentage of children affected by inadequate sleep demonstrates a strong relationship with age throughout childhood, with a more marked increase by age for children ≥12 years of age (Fig 1).

Characteristics of children with and without reported adequate sleep are presented by age group in Table 1. In both groups, children with reported inadequate sleep were more frequently non-Hispanic white, resided in families with education greater than high school and higher income levels, and were more frequently described as having less-than-excellent health compared with children with reported adequate sleep patterns. Disease comorbidities such as atopic conditions, attention-deficit disorder (ADD), or ADHD were more common in children with inadequate sleep. Parents of children with inadequate sleep reported less successful school experiences, with approximately one third having been contacted for a school-related problem and more reporting their child having been bullied by classmates.

Table 2 presents results of the multivariate logistic regression analyses. All models controlled for demographic, child health, school and activities, and family life variables. When covariates were examined independently for their relationship to inadequate sleep, the following variables were associated with greater sleep needs in both age groups: (*a*) presence of 1 or more depressive symptoms, (*b*) less frequent days of physical activity, and living in a home where (*c*) parents argue heatedly or shout, (*d*) on rare occasions respond by hitting or throwing things during family disagreements, or (*e*) perceive that the environment at home, school, or in the community is not always safe. Some variables were exclusively associated with inadequate sleep in the elementary school age group: (*a*) having problems at school and (*b*) fair or poor paternal general health, whereas others were associated with inadequate sleep in the adolescent group only (*a*) an atopic condition, (*b*) frequent or severe headaches, (*c*) less-than-excellent maternal or paternal emotional health, (*d*) parental perception that the child is sometimes harder to care for

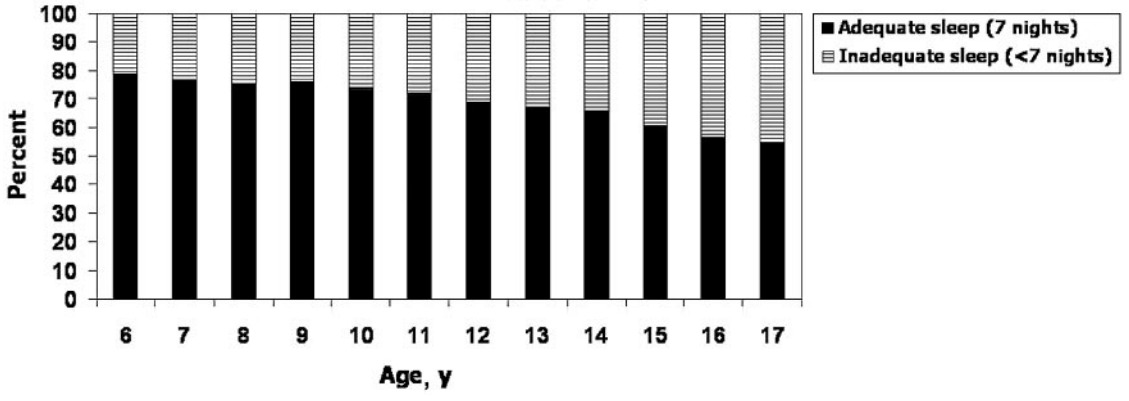


FIGURE 1
Percentage of children with reported inadequate sleep according to year of age ($P < .001$ for trend). Source: 2003 National Survey of Children's Health.

TABLE 1 **Characteristics of Children With and Without Reported Inadequate Sleep According to Age Group**

Variable	Age 6 to 11 y ($N = 23\,764\,177$)		Age 12 to 17 y ($N = 23\,641\,346$)	
	Inadequate Sleep ($N = 5\,828\,973$ [24.5%])	Adequate Sleep ($N = 17\,935\,204$ [75.5%])	Inadequate Sleep ($N = 9\,302\,085$ [39.3%])	Adequate Sleep ($N = 14\,339\,261$ [60.7%])
Demographic characteristics				
Gender				
Male	51.3	51.1	50.1	51.2
Female (reference)	48.7	48.9	49.9	48.8
Race/ethnicity				
Non-Hispanic white (reference)	63.3	59.6	69.8	60.4
Non-Hispanic black	14.9	14.3	12.9[a]	16.3
Hispanic	15.3[a]	18.0	11.3[a]	16.4
Other/mixed race	6.2[a]	8.0	5.9[a]	6.7
Family education level				
Less than high school	7.7	7.9	4.7[a]	8.0
High school graduate	23.5[a]	27.0	22.6[a]	30.1
More than high school (reference)	68.8	65.1	72.7	61.8
Income as % PL				
<100% PL	14.3[a]	16.1	10.9[a]	16.1
100%–199% PL	19.7[a]	21.2	18.0[a]	20.9
200%–399% PL	31.3	30.3	32.3[a]	29.3
≥400% PL (reference)	26.3	22.8	29.7	22.8
PL missing	8.4	9.6	9.0	11.0
Child health				
Health status				
Excellent (reference)	57.3	62.1	56.3	59.1
Very good, good	38.4[b]	34.9	40.3[b]	37.2
Fair, poor	4.3[b]	3.0	3.4	3.6
Comorbid conditions				
Depression/anxiety	5.3[b]	2.9	8.0[b]	6.6
Behavioral/conduct problem	8.7[b]	5.3	6.5	6.3
Developmental delay or physical impairment	3.7	3.8	3.2	3.4
Atopic condition[c]	32.4[b]	29.1	33.6[b]	27.4
Frequent or severe headache	5.9[b]	4.4	10.4[b]	7.9
Learning disability	11.2[b]	9.3	12.2[a]	13.8
ADD/ADHD	9.6 [b]	7.1	10.1	9.5
Reported child behaviors				
Depressive symptoms[d]				
Never (reference)	11.4	19.7	12.2	20.5
Sometimes	73.0[b]	69.8	72.6[b]	66.8
Usually, always	15.6[b]	10.5	15.2[b]	12.7
Overweight	27.5	28.3	11.5[a]	13.4
School and activities				
Having problems at school				
Never (reference)	65.0	72.8	67.6	70.7
Parents contacted	35.0[b]	27.2	32.4[b]	29.3
Bullied by classmates				
Not at all (reference)	56.3	61.5	69.6	69.1
A little	28.7[b]	23.4	19.6[b]	17.4
A lot	15.0	15.2	10.8[a]	13.5
Days of physical exercise (≥20 min/d) during past week				15.6
None	7.0[b]	6.9	15.5[b]	
1–5 d	62.6[b]	55.1	61.3[b]	56.0
6–7 days (reference)	30.4	38.0	23.2	28.4
Television/video time per d				
≤2 h (reference)	55.2	57.6	56.3	52.4
>2 h	44.8[b]	42.4	43.7[a]	47.6
Family life				
Family structure				
2 parents, biological/adopted (reference)	63.5	61.7	57.3	53.8
2-parent stepfamily	9.1	10.2	12.2[a]	13.8
Single mother	23.9	23.1	26.1	26.0
Other	3.5[a]	5.0	4.4[a]	6.4

TABLE 1 **Continued**

Variable	Age 6 to 11 y (N = 23 764 177)		Age 12 to 17 y (N = 23 641 346)	
	Inadequate Sleep (N = 5 828 973 [24.5%])	Adequate Sleep (N = 17 935 204 [75.5%])	Inadequate Sleep (N = 9 302 085 [39.3%])	Adequate Sleep (N = 14 339 261 [60.7%])
Total children in household				
1 (reference)	14.8	14.2	28.6	25.6
2	39.4	40.7	37.3[a]	36.9
≥3	45.9	45.2	34.1[a]	37.5
Parental health				
Mother's general health				
Excellent (reference)	29.2	35.0	27.8	31.5
Very good, good	59.0[b]	55.7	59.8[b]	55.9
Fair, poor	11.8[b]	9.3	12.4	12.6
Mother's emotional health				
Excellent (reference)	28.3	38.5	29.2	37.1
Very good, good	63.1[b]	56.0	62.1[b]	55.7
Fair, poor	8.6[b]	5.5	8.7[b]	7.2
Father's general health				
Excellent (reference)	30.7	37.9	28.6	32.7
Very good, good	62.2[b]	56.4	63.0[b]	58.7
Fair, poor	7.1[b]	5.7	8.4	8.6
Father's emotional health				
Excellent (reference)	34.1	45.2	34.0	41.9
Very good, good	62.0[b]	51.5	61.2[b]	53.8
Fair, poor	3.9[b]	3.3	4.8[b]	4.3
Family stress				
Child harder to care for				
Never (reference)	64.4	73.1	64.5	69.9
Sometimes	28.7[b]	21.5	28.2[b]	23.5
Usually, always	6.9[b]	5.4	7.3[b]	6.7
Argue heatedly or shout				
Never (reference)	17.6	27.0	16.6	23.8
Rarely	34.6[b]	33.9	33.5[b]	34.0
Sometimes, usually, always	47.8[b]	39.2	49.9[b]	42.3
Hitting/throwing things during family disagreements	84.5	90.2	86.5	90.2
Never (reference)	11.5[b]	6.8	10.1[b]	6.9
Rarely	4.0	3.0	3.4	2.9
Sometimes, usually, always				
Parental anger with child				
Never (reference)	15.9	23.9	17.4	25.1
Sometimes	80.7[b]	73.8	77.5[b]	71.7
Usually, always	3.4[b]	2.3	5.1[b]	3.2
Environmental safety[e]				
Always (reference)	33.3	41.9	26.5	35.1
Usually	52.3[b]	43.7	59.6[b]	47.8
Sometimes, never	14.4[b]	14.4	13.9	17.1

[a] Significantly associated with lesser impaired sleep, relative to reference category, in bivariate analysis.
[b] Significantly associated with greater impaired sleep, relative to reference category, in bivariate analysis.
[c] Respondent report of ≥1 of the following conditions: asthma, hay fever or respiratory allergy, eczema or skin allergy.
[d] Respondent report of ≥1 of the following during the past month: child feels worthless or inferior, unhappy, sad or depressed, stubborn, sullen or irritable, or withdrawn.
[e] Respondent report of ≥1 of the following areas of concern for child's safety: at school, neighborhood, or home.

than other children, and (*e*) parental anger with the child. Living in a family with reported income <400% of the federal poverty level (PL) was associated with significantly lower odds of inadequate sleep, even after controlling for potentially confounding variables. In addition, >2 hours of television viewing per day, diagnosis of learning disability, and being victimized by classmate bullying behavior were associated with significantly lower odds of inadequate sleep in the adolescent group.

DISCUSSION

The neuroscientist Robert Stickgold warns that because critical reparative and integrative processes ". . .occur exclusively during sleep and can't be reproduced when we are awake, the consequences of losing them look more and more terrifying. . . ."[29] The independent nonprofit National Sleep Foundation concluded from its 2004 *Sleep in America* poll that a remarkable number of children age 10 and younger have some kind of sleep

TABLE 2 **Adjusted ORs for Inadequate Sleep for Children Aged 6 to 11 and 12 to 17 Years**

	Age 6–11 y			Age 12–17 y		
	OR	95% CI	*P*	OR	95% CI	*P*
Demographic characteristics						
Race/ethnicity			<.01			<.001
Non-Hispanic white (reference)	1.00			1.00		
Non-Hispanic black	1.02	0.83–1.25		0.73	0.60–0.89	
Hispanic	0.80	0.66–0.97		0.71	0.59–0.86	
Other/mixed race	0.69	0.53–0.90		0.77	0.60–0.99	
Family education level			.02			<.001
Less than high school	1.01	0.71–1.43		0.74	0.49–1.11	
High school graduate	0.81	0.70–0.94		0.68	0.60–0.77	
More than high school (reference)	1.00			1.00		
Income as % PL			.01			<.001
<100% PL	0.68	0.52–0.88		0.49	0.38–0.64	
100%-199% PL	0.77	0.64–0.91		0.79	0.67–0.93	
200%-399% PL	0.91	0.80–1.03		0.89	0.80–0.99	
≥400% PL (reference)	1.00			1.00		
Child health						
Atopic condition[a]			NS			.002
Yes				1.17	1.06–1.29	
No (reference)				1.00		
Frequent or severe headache			NS			.01
Yes				1.27	1.05–1.53	
No (reference)				1.00		
Learning disability			NS			<.001
Yes				0.68	0.58–0.78	
No (reference)				1.00		
Depressive symptoms[b]			<.001			<.001
Never (reference)	1.00			1.00		
Sometimes	1.38	1.17–1.63		1.56	1.36–1.79	
Usually, always	1.67	1.32–2.12		1.43	1.17–1.75	
School and activities						
Having problems at school			.03			NS
Never (reference)	1.00					
Parents contacted	1.16	1.02–1.32				
Bullied by classmates			NS			.01
Not at all (reference)				1.00		
A little				0.91	0.81–1.02	
A lot				0.79	0.66–0.93	
Days physical education during past week			<.001			<.001
None	1.10	0.85–1.42		1.16	1.00–1.35	
1–5	1.43	1.28–1.60		1.33	1.19–1.49	
6–7 (reference)	1.00			1.00		
Television/video time per d			NS			<.001
≤2 h (reference)				1.00		
>2 h				0.84	0.76–0.92	
Family life						
Mother's emotional health			NS			.04
Excellent (reference)				1.00		
Very good, good				1.20	1.03–1.39	
Fair, poor				1.32	0.98–1.77	
Father's general health			.04			NS
Excellent (reference)	1.00					
Very good, good	1.14	0.99–1.32				
Fair, poor	1.41	1.06–1.88				
Father's emotional health			NS			.03
Excellent (reference)				1.00		
Very good, good				1.18	1.02–1.36	
Fair, poor				1.41	1.04–1.92	
Family stress						
Child harder to care for			NS			.001
Never (reference)				1.00		
Sometimes				1.24	1.10–1.39	
Usually, always				1.26	0.96–1.66	

TABLE 2 **Continued**

	Age 6–11 y			Age 12–17 y		
	OR	95% CI	*P*	OR	95% CI	*P*
Argue heatedly or shout			.007			.005
Never (reference)	1.00			1.00		
Rarely	1.17	1.01–1.35		1.10	0.96–1.25	
Sometimes, usually, always	1.28	1.10–1.49		1.24	1.08–1.42	
Hitting, throwing things			.002			<.001
Never (reference)	1.00			1.00		
Rarely	1.40	1.16–1.70		1.41	1.17–1.70	
Sometimes, usually, always	1.19	0.81–1.75		1.19	0.87–1.63	
Parental anger with child			NS			.006
Never (reference)				1.00		
Sometimes				1.15	1.02–1.30	
Usually, always				1.61	1.16–2.23	
Environmental safety[c]			.002			<.001
Always safe (reference)	1.00			1.00		
Usually safe	1.23	1.09–1.38		1.35	1.22–1.49	
Sometimes, never safe	1.06	0.86–1.32		1.05	0.87–1.25	

NS indicates not significant. Each model controls for demographic characteristics, child health, school and activities, and family life variables.

[a] Respondent report of 1 of the following conditions: asthma, hay fever or respiratory allergy, eczema or skin allergy.

[b] Respondent report of ≥1 of the following during the past month: child feels worthless or inferior, unhappy, sad or depressed, stubborn, sullen or irritable, or withdrawn.

[c] Respondent report of ≥1 of the following areas of concern for child's safety: at school, neighborhood, or home.

problem,[9] three quarters of parents are dissatisfied about children's sleep, and few pediatric providers inquire about or follow-up on sleep complaints; their more recently released adolescent data contain similar concerns.[10] Carskadon[30] refers to sleep as "the forgotten country" and calls for attention to the "sleeping half of children's lives."

Is such alarm warranted? In our analysis, parents in a national random sample reported that 31.9% of their children experienced ≥1 night of inadequate sleep during the previous week. These children experienced health-related deficits associated with selected demographic, child, family, and environmental factors. This is consistent with growing evidence for deleterious effects of even occasional lapses in recommended amounts of sleep.

Acute sleep deprivation and chronic sleep disorders result in behavioral and performance deficits in school-aged children.[2,31–34] Adolescents' erratic sleep patterns are fostered by pubertal changes in hormone secretion making it difficult to fall asleep before 11 PM[7]; yet early school start times compel them to be in class before 8 AM.[5] Weekday and weekend variations result in prolonged delayed sleep onset, insomnia, and daytime sleepiness throughout the week[35] along with impaired mood, behavioral control, and academic performance.[7,36]

Ethnocultural and Socioeconomic Differences

Impact of sleep problems on children and families transcends all cultures.[37] Contrary to earlier studies[8,16,38] identifying minority and poorer children at greater risk, our data suggest that parents of non-Hispanic white children and those who have higher income and greater than high school education more frequently report the perception of inadequate sleep in their children. Roberts[39] examined differences in sleep complaints among 5423 American adolescents of African, Chinese, Mexican, Central American, and Anglo descent and concluded minority status may affect risk for sleep problems. Primary school children in China averaged 9.3 vs 10.2 hours of sleep compared with US children and reported daytime sleepiness.[40] Cross-sectional analysis of child journals and caregiver questionnaires for 755 children aged 8 to 11 years showed that at all ages minority boys slept significantly less compared with minority girls and all nonminority children.[8] A parent-report survey of 472 children in 1 US city showed an inverse association between socioeconomic status and both parasomnias and noisy sleep.[2] Exploration of sleep by ethnicity and socioeconomics remains in its infancy. Comparisons across studies are hampered by differences in definitions and data sources.

Sleep and Comorbidity

In our analysis, the relationship between inadequate sleep and mood disorders was present in both younger and older children. Children with depression subjectively reported poor and inadequate sleep when compared with controls; however, 1 study using objective electroencephalogram data failed to validate this relationship.[41] When sleep architecture was studied in depressed, unmedicated children compared with healthy controls, only depressed older boys had significant sleep disturbance.[42]

Consistent with the literature, in this study adolescents with atopic conditions and headache were more likely to have inadequate sleep compared with children without these conditions. However, this finding did not

hold true for younger children. Children in remission phase of atopic dermatitis evaluated by polysomnography demonstrate significantly disturbed sleep symptoms.[43] As many as 64% of asthmatic children report 3 nocturnal awakenings per week.[44] Individuals with allergic rhinitis sleep poorly and have sleep-disordered breathing and subsequent daytime sleepiness.[45,46] Although children with migraine headaches subjectively experienced more sleep problems than did healthy control children,[47,48] more objective actigraphy did not show differences in sleep parameters.[49]

Our data failed to demonstrate an association between inadequate sleep and ADHD in either age group in multivariate models. Studies relying on parental report of sleep behavior[18,38,50] support an association between a diagnosis of ADHD and sleep problems in children. Parents of children with ADHD report sleep problems in 25% to 50% of these children,[20] but these findings are not supported when more objective measurements such as polysomnography are used.[51]

Family Health and Social Factors

In both age groups, inadequate sleep was associated with family conflict; in teens it was further associated with parental emotional health, being perceived as a difficult child, and parental anger. Sleep issues are known to exist with child abuse and family violence.[52,53] Our study makes the connection with inadequate sleep much earlier in the violence spectrum. It may be that perceived inadequate sleep is an alert for suboptimal family functioning and should trigger assessment, referral, and early intervention. Inadequate sleep was also associated with not feeling safe in school or neighborhood. The National Institute of Mental Health reports a significant increase in US children as witnesses to or victims of community violence[54] with resulting physical and psychological effects.[55] Regular use of brief sleep assessment tools[7] can lead to addressing sleep issues and their underlying causes.

Limitations

These NSCH cross-sectional data limit interpretation to association. All bivariate and multivariate associations described in the text and displayed in the tables are bidirectional and reflect simultaneous relationships between independent variables and the dependent variable. Therefore, neither cause nor causal direction can be determined. In addition, sleep information is derived from parental response to 1 question concerning adequacy of a child's sleep during the past week. The survey does not provide information about perceived or diagnosed causes of inadequate sleep, whether it was a usual or unusual occurrence, or the norms by which each parent judged sleep. Nevertheless, prevalence of inadequate sleep and its effects in this large national sample are consistent with reports of epidemiologic sleep studies.[9,10] Because evidence is accumulating concerning the health risks of inadequate sleep at all ages, future surveys should explore sleep in greater detail.

CONCLUSIONS

Sleep health is an important but underrecognized component of wellness in children. Sleep impairment may provide a critical alert for primary care providers to search for undiagnosed physical or psychological comorbidity, suboptimal coping, family dysfunction, or threats in school or community. Conversely, when any of these conditions and/or situations is known to be present, sleep impairment may be a comorbid symptom that needs to be addressed. Sleep health and its assessment should be a fundamental aspect of clinical prevention.

REFERENCES

1. Chervin RD, Archbold KH, Panahi P, Pituch KJ. Sleep problems seldom addressed at two general pediatric clinics. *Pediatrics.* 2001;107:1375–1380
2. Stein MA, Mendelsohn J, Obermeyer WH, Amromin J, Benca R. Sleep and behavior problems in school-aged children. *Pediatrics.* 2001;107(4). Available at: www.pediatrics.org/cgi/content/full/107/4/e60
3. Wilkoff W. Sleep need in children. *Pediatrics.* 2003;112:1463–1464
4. Blunden S, Lushington K, Lorenzen B, Ooi T, Fung F, Kennedy D. Are sleep problems under-recognised in general practice? *Arch Dis Child.* 2004;89:708–712
5. Lamberg L. Pediatric sleep medicine comes of age. *JAMA.* 2005;293:2327–2329
6. Hoban TF. Sleep and its disorders in children. *Semin Neurol.* 2004;24:327–340
7. Owens JA, Witmans M. Sleep problems. *Curr Probl Pediatr Adolesc Health Care.* 2004;34:154–179
8. Spilsbury JC, Storfer-Isser A, Drotar D, et al. Sleep behavior in an urban US sample of school-aged children. *Arch Pediatr Adolesc Med.* 2004;158:988–994
9. National Sleep Foundation. 2004 Sleep in America poll. Available at: www.sleepfoundation.org/_content//hottopics/2004SleepPollFinalReport.pdf. Accessed April 17, 2006
10. National Sleep Foundation. Adolescent sleep needs and patterns: research report and resource guide. Available at: www.sleepfoundation.org/_content/hottopics/sleep_and_teens_report1.pdf. Accessed April 17, 2006
11. Heussler HS. 9. Common causes of sleep disruption and daytime sleepiness: childhood sleep disorders II. *Med J Aust.* 2005;182:484–489
12. Howard BJ, Wong J. Sleep disorders. *Pediatr Rev.* 2001;22:327–342
13. Anders T, Sadeh A, Appareddy V. Normal sleep in neonates and children. In: Ferber R, Kryger M, eds. *Principles and Practice of Sleep Medicine in the Child*. Philadelphia, PA: WB Saunders; 1995:7–18
14. Yarcheski A, Mahon NE. A study of sleep during adolescence. *J Pediatr Nurs.* 1994;9:357–367
15. Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics.* 2003;111:302–307
16. Roberts RE, Roberts CR, Chen IG. Ethnocultural differences in sleep complaints among adolescents. *J Nerv Ment Dis.* 2000;188:222–229
17. Fallone G, Seifer R, Acebo C, Carskadon MA. How well do

school-aged children comply with imposed sleep schedules at home? *Sleep.* 2002;25:739–745
18. Owens JA, Maxim R, Nobile C, McGuinn M, Msall M. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med.* 2000;154:549–555
19. Marcotte AC, Thacher PV, Butters M, Bortz J, Acebo C, Carskadon MA. Parental report of sleep problems in children with attentional and learning disorders. *J Dev Behav Pediatr.* 1998;19:178–186
20. Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 1998;37:637–646
21. Fallone G, Owens JA, Deane J. Sleepiness in children and adolescents: clinical implications. *Sleep Med Rev.* 2002;6:287–306
22. Dahl RE, Ryan ND, Matty MK, et al. Sleep onset abnormalities in depressed adolescents. *Biol Psychiatry.* 1996;39:400–410
23. Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S, Sampson HA, Lupo M. Sleep disturbances in children with atopic dermatitis. *Arch Pediatr Adolesc Med.* 1995;149:856–860
24. Sadeh A, Horowitz I, Wolach-Benodis L, Wolach B. Sleep and pulmonary function in children with well-controlled, stable asthma. *Sleep.* 1998;21:379–384
25. Kogan MD, Newacheck PW. Introduction to the volume on articles from the National Survey of Children's Health. *Pediatrics.* 2007;119(suppl 1):S1–S3
26. Blumberg SJ, Olson L, Frankel M, Osborn L, Srinath KP, Giambo P. Design and operation of the National Survey of Children's Health, 2003. *Vital Health Stat 1.* 2005;(43):1–124
27. American Academy of Pediatrics, Committee on Public Education. Children, adolescents, and television. *Pediatrics.* 2001;107:423–426
28. *SUDAAN Language Manual, Release 9.0.* Research Triangle Park, NC: Research Triangle Institute; 2004
29. Lambert C. Deep into sleep. *Harvard Magazine.* 2005;107:25–33
30. Carskadon MA. The sleep of America's children. National Sleep Foundation. Available at: www.sleepfoundation.org/hottopics/index.php?secid=11&id=82. Accessed December 20, 2005
31. Dahl RE. The impact of inadequate sleep on children's daytime cognitive function. *Semin Pediatr Neurol.* 1996;3:44–50
32. Smedje H, Broman JE, Hetta J. Short-term prospective study of sleep disturbances in 5–8-year-old children. *Acta Paediatr.* 2001;90:1456–1463
33. Fallone G, Acebo C, Arnedt JT, Seifer R, Carskadon MA. Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. *Percept Mot Skills.* 2001;93:213–229
34. Smedje H, Broman JE, Hetta J. Associations between disturbed sleep and behavioural difficulties in 635 children aged six to eight years: a study based on parents' perceptions. *Eur Child Adolesc Psychiatry.* 2001;10:1–9
35. Hoban TF, Chervin RD. Assessment of sleepiness in children. *Semin Pediatr Neurol.* 2001;8:216–228
36. Dahl RE. Pathways to adolescent health sleep regulation and behavior. *J Adolesc Health.* 2002;6:175–184
37. Owens JA. Introduction: culture and sleep in children. *Pediatrics.* 2005;115:201–203
38. Stein MA. Unravelling sleep problems in treated and untreated children with ADHD. *J Child Adolesc Psychopharmacol.* 1999;9:157–168
39. Roberts RE, Roberts CR, Chen IG. Ethnocultural differences in sleep complaints among adolescents. *J Nerv Mental Dis.* 2000;188;222–229
40. Liu X, Liu L, Owens JA, Kaplan DL. Sleep patterns and sleep problems among schoolchildren in the United States and China. *Pediatrics.* 2005;115:241–249
41. Bertocci MA, Dahl RE, Williamson DE, et al. Subjective sleep complaints in pediatric depression: a controlled study and comparison with EEG measures of sleep and waking. *J Am Acad Child Adolesc Psychiatry.* 2005;44:1158–1166
42. Robert JJ, Hoffmann RF, Emslie GJ, et al. Sex and age differences in sleep macroarchitecture in childhood and adolescent depression. *Sleep.* 2006;29:351–358
43. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with atopic dermatitis. *Arch Pediatr Adolesc Med.* 1999;153:249–253
44. Turner-Warwick M. Epidemiology of nocturnal asthma. *Am J Med.* 1988;85(1B):6–8
45. Craig TJ, McCann JL, Gurevich F, Davies MJ. The correlation between allergic rhinitis and sleep disturbance. *J Allergy Clin Immunol.* 2004;114(5 suppl):S139–S145
46. Desager KN, Nelen V, Weyler JJ, De Backer WA. Sleep disturbance and daytime symptoms in wheezing school-aged children. *J Sleep Res.* 2005;14:77–82
47. Miller VA, Palermo TM, Powers SW, Scher MS, Hershey AD. Migraine headaches and sleep disturbances in children. *Headache.* 2003;43:362–368
48. Carotenuto M, Guidetti V, Ruju F, Galli F, Tagliente FR, Pascotto A. Headache disorders as risk factors for sleep disturbances in school aged children. *J Headache Pain.* 2005;6:268–270
49. Bruni O, Russo PM, Violani C, Guidetti V. Sleep and migraine: an actigraphic study. *Cephalalgia.* 2004;24:134–139
50. Ring A, Stein D, Barak Y, et al. Sleep disturbances in children with attention-deficit/hyperactivity disorder: a comparative study with healthy siblings. *J Learn Disabil.* 1998;31:572–578
51. Sangal RB, Owens JA, Sangal J. Patients with attention-deficit/hyperactivity disorder without observed apneic episodes in sleep or daytime sleepiness have normal sleep on polysomnography. *Sleep.* 2005;28:1143–1148
52. McFarlane JM, Groff JY, O'Brien JA, Watson K. Behaviors of children who are exposed and not exposed to intimate partner violence: an analysis of 330 black, white, and Hispanic children. *Pediatrics.* 2003;112(3). Available at: www.pediatrics.org/cgi/content/full/112/3/e202
53. Wells RD, McCann J, Adams J, Voris J, Ensign J. Emotional, behavioral, and physical symptoms reported by parents of sexually abused, nonabused, and allegedly abused prepubescent females. *Child Abuse Negl.* 1995;19:155–163
54. Richters JE, Martinez P. The NIMH community violence project: I. Children as victims of and witnesses to violence. *Psychiatry.* 1993;56:7–21
55. Martinez P, Richters JE. The NIMH community violence project: II. Children's distress symptoms associated with violence exposure. *Psychiatry.* 1993;56:22–35

Sleepless in America: Inadequate Sleep and Relationships to Health and Well-being of Our Nation's Children

Arlene Smaldone, Judy C. Honig and Mary W. Byrne

Pediatrics 2007;119;S29
DOI: 10.1542/peds.2006-2089F

Sleepless in America: Inadequate Sleep and Relationships to Health and Well-being of Our Nation's Children

Arlene Smaldone, Judy C. Honig and Mary W. Byrne

Pediatrics 2007;119;S29
DOI: 10.1542/peds.2006-2089F

Talbott et al. Environmental Health (2015) 14:80
DOI 10.1186/s12940-015-0064-1

ENVIRONMENTAL HEALTH

RESEARCH Open Access

Air toxics and the risk of autism spectrum disorder: the results of a population based case–control study in southwestern Pennsylvania

Evelyn O. Talbott[1*], Lynne P. Marshall[1], Judith R. Rager[1], Vincent C. Arena[2], Ravi K. Sharma[3] and Shaina L. Stacy[4]

Abstract

Background: Autism spectrum disorders (ASD) constitute a major public health problem affecting one in 68 children. There is little understanding of the causes of ASD despite its serious social impact. Air pollution contains many toxicants known to have adverse effects on the fetus. We conducted a population based case–control study in southwestern Pennsylvania to estimate the association between ASD and 2005 US EPA modeled NATA (National Air Toxics Assessment) levels for 30 neurotoxicants.

Methods: A total of 217 ASD cases born between 2005 and 2009 were recruited from local ASD diagnostic and treatment centers. There were two different control groups: 1) interviewed controls ($N = 224$) frequency matched by child's year of birth, sex and race with complete residential histories from prior to pregnancy through the child's second birthday, and 2) 5,007 controls generated from a random sample of birth certificates (BC controls) using residence at birth. We used logistic regression analysis comparing higher to first quartile of exposure to estimate odds ratios (ORs) and 95 % confidence intervals (CI), adjusting for mother's age, education, race, smoking status, child's year of birth and sex.

Results: Comparing fourth to first quartile exposures for all births, the adjusted OR for styrene was 2.04 (95 % CI = 1.17–3.58, $p = 0.013$) for the interviewed case–control analysis and 1.61 (95 % CI = 1.08-2.40, $p = 0.018$) for the BC analysis. In the BC comparison, chromium also exhibited an elevated OR of 1.60 (95 % CI = 1.08-2.38, $p = 0.020$), which was similarly elevated in the interviewed analysis (OR = 1.52, 95 % CI = 0.87–2.66). There were borderline significant ORs for the BC comparison for methylene chloride (OR = 1.41, 95 % CI = 0.96–2.07, $p = 0.082$) and PAHs (OR = 1.44, 95 % CI = 0.98–2.11, $p = 0.064$).

Conclusions: Living in areas with higher levels of styrene and chromium during pregnancy was associated with increased risk of ASD, with borderline effects for PAHs and methylene chloride. These results are consistent with other studies. It is unclear, however, whether these chemicals are risk factors themselves or if they reflect the effect of a mixture of pollutants. Future work should include improved spatiotemporal estimates of exposure to air toxics, taking into account the dynamic movement of individuals during daily life.

Keywords: Air toxics, Autism spectrum disorder, Case–control study, Chromium, Geographic information system, Styrene

* Correspondence: eot1@pitt.edu
Evelyn O. Talbott and Lynne P. Marshall are joint first authors.
[1]Department of Epidemiology, University of Pittsburgh, Graduate School of Public Health, 130 DeSoto Street, A526 Crabtree, Pittsburgh, PA 15261, USA
Full list of author information is available at the end of the article

Background

Autism spectrum disorders (ASD) constitute a major public health problem, affecting approximately one in every 68 children and their families [1]. ASDs are brain development disorders usually diagnosed in childhood and characterized by impaired social interaction and communication, and by restricted and repetitive behaviors [2]. In many cases, individuals with ASD cannot live independently and may require lifetime assistance from a family member or caregiver [3]. The families of children with ASD are at an increased risk for mental and physical health problems, parenting stress, financial strain, divorce, and overall lower family well-being [3]. Because ASDs are lifelong conditions for which there is no cure and for which treatment options are limited, there is a need to explore additional potential risk factors for these disorders.

Despite its serious social impact [4], the causes of autism are poorly understood, but both genetic (10–20 %) and environmental factors are thought to be involved. Researchers have noted several risk factors related to ASD including advanced maternal and/or paternal age, maternal smoking history, low birth weight, short gestational duration, and hypoxia during childbirth [5]. In addition, environmental factors, including constituents of air pollution, have been found to be related to an increased risk of autism [6, 7]. These include: $PM_{2.5}$, ozone, NO_2, pesticides, heavy metals, solvents, and diesel exhaust [7–16].

Although there are differences in the time periods of the investigations, geographical regions under study and the exposure assessments, a growing number of studies suggest a potential role of ASD and air pollution. Recently, several investigations have focused on ASD risk and ambient criteria air pollutants (traffic related and/or from industry) [12–16]. Volk et al. (2011, 2013) examined the relationship between traffic-related air pollution and autism in California in two population based case–control studies from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. The first reported increased risk among those living within 1,000 feet of a major freeway [12], and the second found that increased autism risk was associated with exposure to model-based indicators of traffic-related air pollutant (TRP) mixture as well as regional measures of NO_2, $PM_{2.5}$, and PM_{10} [13]. Becerra et al. also noted increased ASD risk per interquartile range increases of ozone, $PM_{2.5}$, NO, and NO_2 [14].

To date, there have been three case–control studies of ASD risk that utilized data from the National Air Toxics Assessment (NATA) to examine exposure to specific neurological toxicants, developmental toxicants, or suspected endocrine disruptors during pregnancy [17–19]. NATA is a US EPA developed database with modeled annual average concentrations of hazardous air pollutants (HAPs) at the state, county, and census tract levels. To model annual average ambient concentrations of air toxics for each census tract, NATA assumes Gaussian air dispersion and uses overlapping spatial grids. Model inputs include locations and rates of pollutant emissions from point, non-point, and mobile sources, as well as secondary-pollutant formation and meteorological data. NATA assessments have been released every three years from 1996 until 2005 [20]. These studies were conducted in various regions of the US and involved time periods between 1990 and 2002. In their investigations, Windham et al. and Kalkbrenner et al. reported that increased ASD risk was associated with higher levels of exposure to groups of heavy metals and chlorinated solvents [19] and to the individual compounds methylene chloride, quinolone, and styrene [17]. Roberts et al. (2013) also noted associations between ASD risk and exposure to overall metals and methylene chloride, as well as lead, manganese and diesel particulate matter [18].

Von Ehrenstein et al. (2014) considered the risk of autistic disorder related to ground level measured exposure to monitored ambient air toxics from urban emissions during the pregnancy period [21]. Birth records were linked to California Department of Developmental Services records of children diagnosed with primary ASD compared to all other births as controls ($N = 768$). ASD risk was increased per interquartile range increase in average concentrations during pregnancy for several correlated toxics, including 1,3-butadiene, meta/para xylene, other aromatic solvents, PERC and formaldehyde, after adjustment for mother's age, race/ethnicity, education, insurance type, parity, sex and birth year [21].

Given these few epidemiological investigations and the heavy industrial background of southwestern Pennsylvania, the objective of the current study was to conduct an exploratory case–control study in this area to assess if neurotoxic air pollutants, as modeled by NATA, were associated with the risk of ASD. We focused on suspect agents found in the previous three investigations which used NATA data and evaluated whether there was an increased risk of ASD associated with higher exposures to these *a priori* agents: arsenic, cadmium, chromium, lead, mercury, manganese, nickel, styrene, trichloroethylene, methylene chloride, vinyl chloride, and diesel particulate matter. Further, we examined additional compounds identified as neurotoxicants, endocrine disruptors, or developmental toxicants by the US EPA [20].

Methods

This study was approved by the University of Pittsburgh Institutional Review Board (IRB number PRO10010240).

Ascertainment of cases

Cases of ASD for this study were children born between January 1, 2005 and December 31, 2009 in Allegheny, Armstrong, Beaver, Butler, Washington, or Westmoreland County in southwestern Pennsylvania and who were currently residing in the six-county area. Our goal was to enroll approximately half of the prevalent cases among this birth cohort. Based on 23,399 births in 2007 in the six county area [22] and a prevalence of ASD of 6 per 1,000 (one in 166), we estimated that 140–141 children per year would be diagnosed with ASD in the study area. We anticipated enrolling half (70–71) of these children each year to result in 250 cases during the 3½ year period of the study.

There is no autism registry in Pennsylvania, and therefore no centralized agency that could be accessed for permission to contact parents of children with ASD for the purposes of conducting a study. Our investigation used an extensive outreach campaign to recruit ASD cases from a combination of 1) ASD specialty diagnostic and treatment centers, 2) private pediatric and psychiatry practices, 3) school-based special needs programs (starting at age 5), and 4) autism support groups. Per our IRB guidelines, we were not allowed to directly contact parents of children with ASD. Therefore, we provided informational packets to these agencies and organizations with a letter, contact sheet and pre-addressed envelope to be returned to our office, and these agencies mailed the information to families with ASD. When a contact sheet was returned, we were permitted to contact the mother to describe the study and request consent to participate.

A case of ASD was defined as any child 1) who scored a 15 or above on the Social Communication Questionnaire (SCQ), a positive screen for the presence of autistic features, and 2) for whom there was written documentation, including ADOS or other test results, of a diagnosis of an ASD from a child psychologist or psychiatrist. Cases were not included in the study if the child was adopted, parents were not English speaking, or a parent was not available for interview. A total of 217 cases were consented and interviewed for the study.

Ascertainment of controls

The study was designed to have two different sets of controls. The first control group (interviewed controls) was recruited from a random selection of 5007 births weighted by sex (4:1 male:female) from the Pennsylvania Department of Health (PA DOH) state birth registry files for 2005 to 2009 in the six-county area. Interviewed controls were frequency matched to the cases on year of birth, sex, and race. We recruited through a direct letter appeal signed by the Pennsylvania Secretary of Health. The rules for both the PADOH IRB and that of the University of Pittsburgh mandated that there would be no direct contact with potential controls, except for the opportunity to return an envelope and contact sheet indicating refusal to be in the study or an indication that the parent was interested in enrolling his or her child in the study by providing contact information. We requested a postal service return to sender, address correction requested. However, since we used an address from the birth certificate that was several years old, it is likely that many of the letters were never delivered to the intended resident or were simply ignored, making it difficult to determine a true response rate.

After we obtained informed consent, parents were screened for inclusion criteria and administered the SCQ for their child. Children with an SCQ >15 or with a reported diagnosis of ASD were not included as controls. Other exclusion criteria were the same as those for cases. The first control group consisted of 226 eligible controls that were consented and interviewed.

For each of the cases and the interviewed controls, a personal interview with the mother was conducted by trained interviewers using a structured questionnaire, adapted from the CDC's Study to Explore Early Development (SEED). The questionnaire included parental demographic and socioeconomic information, a detailed residential history, maternal and paternal occupational history, family history of ASD, smoking history, maternal reproductive and pregnancy history, and child's medical history. Data was obtained on all residential addresses and the corresponding start and end dates that the mother/child lived at those addresses from three months prior to last menstrual period (LMP) until the child's second birthday.

The second control group (birth certificate or BC controls) consisted of a random sample of births occurring from 2005 to 2009 for the six county area of study, weighted with a male to female ratio of 4:1 and year of birth. Birth certificate information on the cases and controls, consisting of residence at birth, age of mother, smoking history, maternal education, race and other infant characteristics, was then used for the second case–control analysis. Of the total sample of 5,007 birth certificates, 16 were identified as being in our case (ASD) population and were removed from the control group.

Exposure assessment

Exposure to ambient hazardous air pollution concentrations was estimated using modeled data from the 2005 NATA assessment. The 2005 NATA estimates are an annual average by census tract and were downloaded from the US EPA website (http://www.epa.gov/ttn/atw/nata2005/tables.html accessed April 16, 2014). Out of the 177 air toxics available through NATA, we examined the distribution, variability, and correlations of 37 air toxics characterized as having neurological, developmental or

endocrine-disrupting effects by one of the previous studies [17–19] or the US EPA [20]. Seven chemicals (carbon tetrachloride, chloroform, ethylene dibromide, ethylene dichloride, hexachlorobenzene, methyl chloride, and PCBs) were excluded from further analysis due to little diversity in their distributions within the six-county area, leaving a total of 30 NATA compounds for analysis.

For the analyses of the interviewed cases and controls, the residential addresses obtained during the interview were geocoded to an X, Y coordinate using ArcGIS (version 10.1; ESRI Inc., Redlands, CA) and verified manually. When an address could not be successfully geocoded in ArcGIS, other methods were used, including MapQuest Latitude/Longitude Finder (http://developer.mapquest.com/web/tools/lat-long-finder). Year 2000 census tracts (11 digit FIPS codes) for each address were assigned using ArcGIS 10.1, linking to 2009 Tiger Line files for the 2000 United States census. We calculated person-specific exposure estimates for each of the air toxic compounds, taking into account the locations of and changes in residence and the time spent at each residence. For each child, average exposure estimates were computed for the time periods of pregnancy, first year of life, and second year of life. Two participants who lived at a residence outside of the United States for which no NATA data was available were excluded from analysis, leaving an analytic group of 217 cases and 224 controls.

For the birth certificate data analysis, NATA concentrations were linked to census tract of residence at birth. All births that could be linked to a PA DOH birth certificate either contained the census tract of birth or the zip code of birth. When only zip code was provided, the 2010 ZCTA shapefile was used to calculate the geographical center of each zip code in ArcGIS 10.2. Then, each ZCTA centroid was spatially linked to the 2000 census tract that contains it. Of the 217 cases, one of the births could not be linked to its birth certificate, 187 had a census tract on the birth certificate, and 29 only had a zip code of birth. Of the 5,007 potential controls, 16 births were actually in our case population, 4,194 had a census tract on the birth certificate, and 797 only had a zip code of birth. However, 20 control births could not be assigned a NATA exposure: Eighteen could not be linked to a census tract as the documented zip code was not in the 2010 ZCTA shapefile, and two had census tracts documented on the birth certificate that did not match a census tract in the 2005 NATA database. Therefore, the final population in the analysis of BC controls was 216 cases and 4,971 controls.

Statistical analysis

We used logistic regression to investigate the association between exposure to NATA air pollutants and the risk of autism spectrum disorder. In order to calculate individual odds ratios, quartile cut points were calculated for each of the 30 NATA pollutants. These were based on the distribution among the interviewed controls for use in each respective case–control comparison. The three highest quartiles were individually compared to the lowest quartile. For the interviewed cases and controls, separate logistic regression models were conducted for each pollutant during the pregnancy period and secondarily for the first and second year of life. For the birth certificate control comparison, only residence at the time of birth was available. All analyses were adjusted for maternal age, education, race, smoking, child's birth year and child's sex.

In addition to examining compounds individually, we also grouped compounds by structural properties into three classifications: metals excluding selenium (arsenic, cadmium, chromium, lead, manganese, mercury, and nickel), aromatic solvents (benzene, ethyl benzene, styrene, toluene and xylenes), and chlorinated solvents (methylene chloride, perchloroethylene, trichloroethylene, trichloroethane, and vinyl chloride). Index scores were computed for each of the structural groups of metals, aromatic solvents, and chlorinated solvents by summing the quartiles for the compounds in each group. Similar to what was done for the individual compounds, quartile cut points of these scores were calculated based on the distribution of the index scores among the interviewed controls. Logistic regression models comparing highest quartiles to the lowest quartile were conducted for each of the indices for both the interviewed and BC comparisons, controlling for mother's age, education, race, smoking, child's year of birth and sex. IBM SPSS Statistics 20 and 22 were used for all analyses. No formal adjustment was made for multiple comparisons.

Additionally, we noted a significantly higher number of multiple births reported among cases compared to controls (8.4 % among the cases; 4.0 % and 3.8 % among the interviewed and birth certificate control groups, respectively). As there is a high rate of prematurity and other problems associated with multiple births, we conducted a sensitivity analysis with and without the inclusion of multiple births for both case–control comparisons.

One of the last steps involved a backward multiple logistic analysis of all agents identified as significant in either case–control comparison with adjustment for mother's age, race, education, smoking, child's birth year, and child's sex. This was done in order to consider the most significant effects of NATA compounds while controlling for the same covariates that were used in the previous logistic regression models for individual pollutants.

Finally, air toxics are often correlated with each other, and people are often simultaneously exposed to a complex mixture of air pollutants. In our study, the Spearman correlation matrix revealed that many of the air toxics were

highly correlated ($p < 0.01$). Similar to the methodology detailed by von Ehrenstein et al [21], we conducted a factor analysis to further examine the correlation structure of our set of 30 air toxics. Factors were extracted using Principal Component Analysis (PCA) and rotated using varimax rotation. The eigenvalue >1 rule was used to determine which factors to retain [21].

Results

A total of 299 families returned a contact sheet and were initially consented and screened for this study (see Additional file 1: Figure S1). Of these, 56 did not meet case inclusion criteria. An additional seven were no longer interested in participating when contacted, and 19 failed to complete the entire interview. The final number of interviewed cases was $n = 217$. These individuals met the requirements for SQL screening and confirmation of diagnosis. The referring sources of the 217 ASD cases were as follows: 116 (49 %) were diagnosed from specialty ASD diagnostic and treatment centers/clinics, 47 (21.6 %) were recruited through private pediatric psychology/psychiatry practices/University, 43 (20 %) were recruited through school-based special needs programs, and 11 (5.1 %) were recruited through autism support groups or our website.

During recruitment, informational letters and contact sheets with return envelopes were mailed to 3,254 households (65 % of the random sample of 5,007 potential controls) (see Additional file 1: Figure S2). There were 369 mailings for which we received an address correction and re-mailed the informational packets. Of the 3,254 prospective participants who were sent letters, 143 were returned as a refusal and 2,861 were either return to sender, forwarding order expired, or no response. A total of 250 potential controls returned contact sheets and consent forms. Of these, 24 were ineligible or unable to be further contacted. The final number of eligible controls who were interviewed was 226.

Characteristics of the study population and estimated exposure to NATA air toxics are presented in Tables 1 and 2. Case–control information is presented according to the information source used for each analysis. In Table 1, information obtained from the interview is presented for the 217 cases and 226 interviewed controls, with the exception of information on LBW (low birth weight, <2500 g) and PTB (preterm birth, <37 weeks gestation), which was obtained from the birth certificate. Information from the birth certificate is presented for the 216 cases for which birth certificate information was available and the 4,971 birth certificate controls.

The majority of both cases and controls were born in Allegheny County, the most populated of the six county areas. Mothers of ASD cases were slightly younger overall than mothers of interviewed controls, but were older than the BC controls. More than half of the mothers of both the interviewed cases and controls reported on interview that they had a college degree or greater; the percent of mothers with a college degree was significantly higher among mothers of interviewed controls compared to cases. The mothers of the 4,971 birth certificate controls, however, had less educational attainment than the mothers of cases (birth certificate information). Cigarette smoking at any time from three months prior to pregnancy until birth was higher among mothers of interviewed ASD cases compared to mothers of interviewed controls. Using the birth certificate information, mothers of cases reported smoking less prior or during pregnancy compared to their birth certificate control counterparts. Preterm births among ASD cases were significantly greater compared to both control groups, largely due to a greater percentage of multiple births (see Table 1).

Table 2 presents the single pollutant 25^{th}, 50^{th}, and 75^{th} percentiles of concentrations of selected NATA hazardous air pollutants for 1) interviewed ASD cases and controls during the pregnancy period, and for 2) cases and the BC controls using the residence at the time of birth from the birth certificate. As the exposure was assigned differently for the two groups of cases and controls (using the residential history during the entire pregnancy period from the interview versus the residence at birth from the birth certificate), we compared the distributions. In the comparison of the two data sources for the cases, we found no significant differences (Mann Whitney test). A comparison between the two control groups (interviewed versus BC), however, showed significant differences in the distributions for selenium, styrene, and cyanide; all were higher for the second control group.

Logistic regression results

In the unadjusted logistic regression analysis of the interviewed case–control comparison (not shown), there were statistically significant odds ratios for fourth compared to first quartile of styrene and chromium. PAHs and methanol were of borderline significance for fourth compared to first quartile. For the birth certificate unadjusted analyses (also not shown), associations were statistically significant for toluene third versus first and styrene second versus first quartile. Results were of borderline significance ($p < 0.10$) for second versus first quartile for lead, PAHs, and diesel PM, and third versus first quartile for benzene.

The adjusted odds ratios for the NATA air toxics grouped into quartiles of exposure during pregnancy with the three highest quartiles compared to the first quartile are shown in Figs. 1a-d and 2a-d and Table 3. For the interviewed case–control analyses, only styrene

Table 1 Characteristics of ASD Cases and Controls (interviewed information versus information from birth certificate)[a]

Characteristic	Interviewed		Birth Certificate	
	Cases ($n = 217$)	Controls ($n = 226$)	Cases ($n = 216$)	Controls ($n = 4{,}971$)
	N (%)	N (%)	N (%)	N (%)
Sex:				
Male	169 (77.9)	175 (77.4)	168 (77.8)	3,980 (80.1)
Female	48 (22.1)	51 (22.6)	48 (22.2)	991 (19.9)
Year of birth – n(%)				
2005	43 (19.8)	53 (23.5)	43 (20.0)	1,153 (23.2)
2006	59 (27.2)	44 (19.5)	59 (27.3)	1,151 (23.2)
2007	48 (22.1)	46 (20.4)	48 (22.2)	1,066 (21.4)
2008	37 (17.1)	41 (18.1)	36 (16.7)	888 (17.9)
2009	30 (13.8)	42 (18.6)	30 (13.9)	713 (14.3)
County at birth – n(%)				
Allegheny	131 (60.4)	133 (58.8)	129 (59.7)	2,883 (58.0)
Armstrong	7 (3.2)	2 (0.9)	7 (3.2)	151 (3.0)
Beaver	7 (3.2)	18 (8.0)	7 (3.2)	393 (7.9)
Butler	17 (7.8)	19 (8.4)	18 (8.3)	409 (8.2)
Washington	22 (10.1)	24 (10.6)	21 (9.7)	448 (9.0)
Westmoreland	33 (15.2)	30 (13.3)	34 (15.7)	687 (13.8)
Maternal age (SD) – mean[b]	30.4(5.4)	31.8 (4.7)	30.4 (5.4)	28.5 (6.0)
Paternal age (SD) – mean[2]	32.6 (6.0)	33.6 (5.9)	32.8 (5.8)	31.4 (6.6)
Mother race[d]				
White	194 (89.4)	219 (96.9)	196 (90.7)	4,055 (81.9)
Black	15 (6.9)	4 (1.8)	16 (7.4)	692 (14.0)
Other	2 (0.9)	2 (0.9)	4 (1.9)	205 (4.1)
Mother's education[e]				
< High school graduate	3 (1.4)	2 (0.9)	6 (2.8)	475 (9.6)
High school graduate and some college	95 (43.8)	46 (20.4)	92 (42.6)	2,536 (51.3)
≥ College graduate	119 (54.9)	178 (78.7)	118 (54.6)	1,937 (39.2)
Low birth weight (<2500 g)[f,i] (based on birth certificate)	23 (10.7)	9 (4.0)	23 (10.6)	341 (6.9)
Preterm birth (< 37 weeks)[g,j] (based on birth certificate)	31 (14.8)	20 (9.0)	31 (14.8)	514 (10.6)
Multiple births	18 (8.4)	9 (4.0)	18 (8.4)	189 (3.8)
Maternal Smoking during pregnancy or in 3 months prior to pregnancy[h]				
Yes	54 (24.9)	24 (10.6)	30 (13.9)	1,165 (23.9)
No	163 (75.1)	202 (89.4)	185 (86.0)	3,714 (76.1)

[a]Includes multiples births
[b]Missing 2
[c]Missing 632
[d]Missing 19
[e]Missing 23
[f]Missing 13
[g]Missing 119
[h]Missing 92 controls and 1 case
[i]Missing 1 case
[j]Missing 4 cases and 6 controls
Interview missing information

Table 2 Single pollutant percentiles of concentration (ng/m^3), full pregnancy period, for ASD interviewed cases ($n = 217$) and controls ($n = 224$) and birth certificate cases ($n = 216$) and controls ($n = 4,971$)

Class	Compounds (Concentration In ng/m^3)	Cases (217)			Controls (224)			Cases (216)			Second Controls (4,971)		
		25	50	75	25	50	75	25	50	75	25	50	75
Metal Compounds	Arsenic	1.03	1.14	1.33	0.98	1.11	1.30	1.02	1.13	1.33	1.00	1.13	1.35
	Cadmium	0.13	0.15	0.18	1.13	0.15	0.18	0.13	0.15	0.18	0.12	0.15	0.19
	Chromium	1.59	1.80	2.40	1.54	1.74	2.06	1.58	1.79	2.30	1.55	1.79	2.18
	Mercury	0.04	0.05	0.08	0.04	0.06	0.08	0.04	0.05	0.08	0.04	0.06	0.08
	Manganese	1.71	2.10	2.38	1.78	2.08	2.27	1.66	2.07	2.36	1.71	2.08	2.30
	Nickel	0.79	0.91	1.06	0.82	0.92	1.02	0.78	0.91	1.04	0.79	0.92	1.07
	Lead	3.40	3.83	4.31	3.29	3.84	4.25	3.36	3.79	4.34	3.27	3.81	4.42
	Selenium	0.35	0.45	0.52	0.38	0.47	0.55	0.36	0.46	0.53	0.32	0.46	0.53
Aromatic Solvents	Benzene	870.78	1102.56	1283.58	823.05	1069.07	1252.91	883.78	1091.58	1289.37	823.50	1082.76	1313.56
	Ethyl benzene	98.16	128.00	188.42	87.25	123.49	181.64	97.35	124.72	188.50	85.25	125.73	196.10
	Styrene	25.22	33.46	51.39	22.82	30.82	40.34	24.43	32.46	50.52	23.67	33.53	48.71
	Toluene	1588.52	2034.18	2501.53	1494.39	2008.97	2439.93	1637.27	2027.70	2536.57	1470.03	2032.16	2553.37
	Xylenes	430.15	591.08	864.09	385.16	536.36	816.75	429.88	583.81	865.79	382.52	588.09	897.42
Chlorinated Solvents	Methylene chloride	241.83	266.47	272.42	241.57	265.99	270.82	244.06	266.47	272.48	239.39	266.53	272.60
	1,1,1-Trichloroethane	215.38	230.86	248.70	210.65	227.25	245.87	215.16	230.84	246.74	211.62	230.70	250.15
	Perchloroethylene	99.77	216.12	266.51	100.31	215.36	262.03	100.08	214.81	267.36	93.71	209.17	265.98
	Trichloroethylene	70.59	74.75	82.92	70.04	73.50	81.64	70.55	74.33	82.46	70.03	74.93	84.26
	Vinyl chloride	0.06	0.09	0.12	0.06	0.09	0.11	0.06	0.09	0.12	0.06	0.09	0.12
Other HAPs	Hydrazine	0.04	0.06	0.06	0.06	0.06	0.06	0.04	0.06	0.06	0.04	0.06	0.07
	PAHs	8.85	12.09	15.87	8.65	11.02	14.60	8.85	12.41	15.72	8.34	12.19	15.70
	Diesel PM	291.11	427.28	660.14	255.12	399.98	589.45	296.99	411.34	614.12	253.58	417.56	666.33
	Allyl chloride	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
	Carbon disulfide	1.60	2.35	3.35	1.46	2.35	2.97	1.55	2.35	3.38	1.55	2.38	3.27
	Cresol	3.38	4.11	4.56	3.33	4.02	4.49	3.44	4.11	4.52	3.30	4.08	4.58
	Cumene	0.95	1.38	1.68	0.91	1.20	1.65	0.94	1.37	1.66	0.90	1.32	1.69
	Cyanide	48.02	68.14	93.24	44.19	59.91	88.38	45.72	67.14	93.11	44.92	67.32	95.47
	2,4-Dinitrotoluene	<0.01	0.01	0.01	<0.01	0.01	0.01	<0.01	0.01	0.01	<0.01	0.01	0.01
	Ethylene oxide	3.48	3.98	4.64	3.37	3.96	4.54	3.48	3.94	4.57	3.40	3.97	4.77
	Hexane	100.15	137.65	201.95	88.07	128.22	190.27	99.95	131.03	198.83	84.67	133.28	205.30
	Methanol	197.44	273.58	408.06	183.92	253.36	348.18	191.54	272.65	396.41	189.02	277.16	403.32

quartile four compared to quartile one remained significant after adjustment for covariates. Thus, women living in areas of the highest quartile of styrene exposure during pregnancy had a 2.04 (95 % CI = 1.17–3.58) odds of having an ASD diagnosed child than women living in areas of the lowest quartile of styrene during pregnancy, after adjusting for mother's age, race, education, smoking, child's year of birth, and child's sex. Additional file 1: Table S1 provides the information on associations of NATA compounds for pregnancy, first year, and second year time periods for the interviewed cases and controls. The association with styrene was the only statistically significant associations of all NATA compounds for these periods. During the child's first year of life, the fourth quartile of styrene compared to the first quartile resulted in a significantly elevated odds of ASD (OR = 1.86, 95 % CI = 1.07–3.25). During year two, the OR was elevated but not significant.

As shown in Table 3 and Figs. 2a-d, there were significantly elevated odds ratios for both styrene and chromium for the BC control comparison. Styrene exhibited a significant effect comparing fourth to first quartile (OR = 1.61, 95 % CI = 1.08–2.40, $p = 0.037$). Chromium was also associated with significantly higher odds of having ASD (OR = 1.60, 95 % CI = 1.08–2.38, $p = 0.018$) when comparing the fourth to the first quartile of

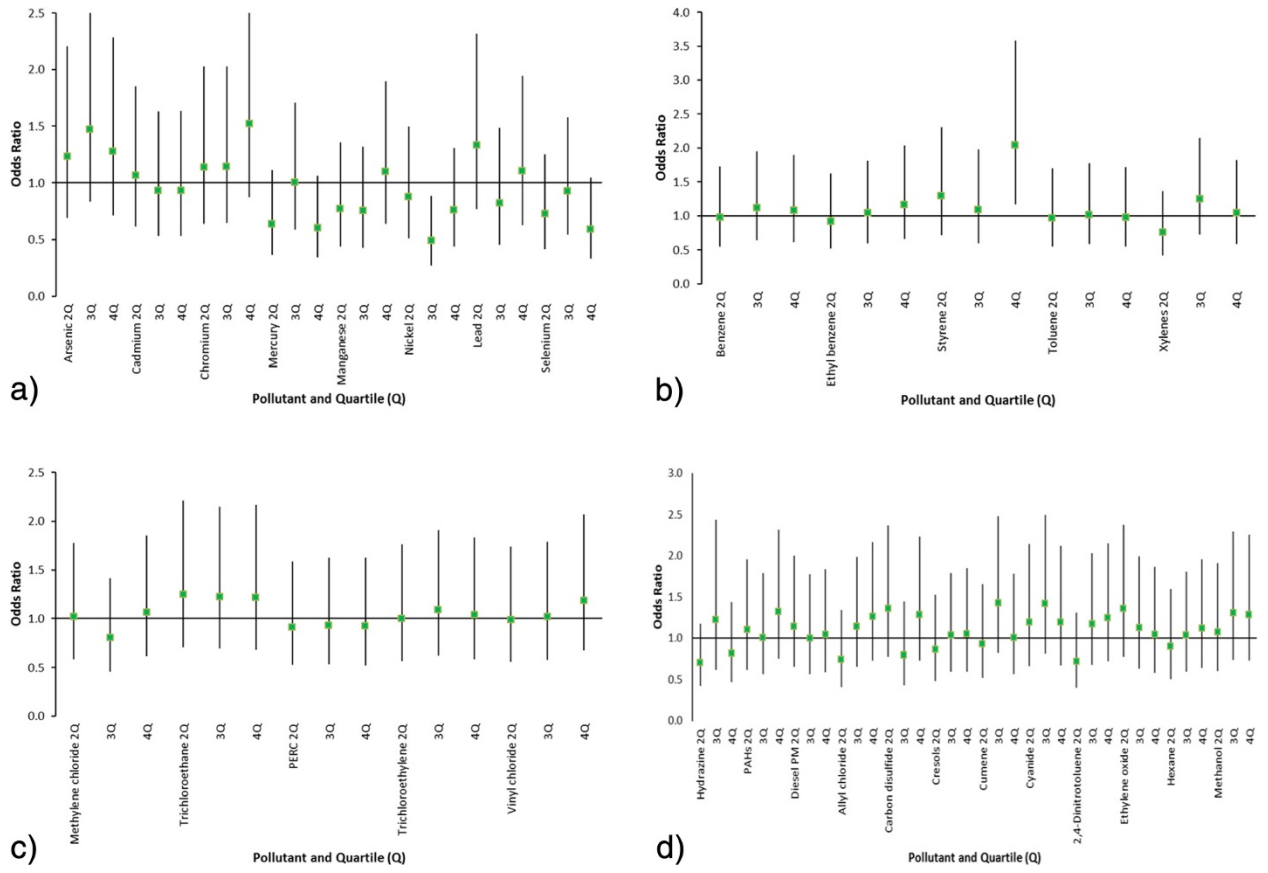


Fig. 1 **a** Adjusted odds ratios with 95 % CI for interviewed ASD cases ($n = 217$) and controls ($n = 224$) associated with quartiles of exposure during pregnancy for metals. **b** Adjusted odds ratios with 95 % CI for interviewed ASD cases ($n = 217$) and controls ($n = 224$) associated with quartiles of exposure during pregnancy for aromatic solvents. **c** Adjusted odds ratios with 95 % CI for interviewed ASD cases ($n = 217$) and controls ($n = 224$) associated with quartiles of exposure during pregnancy for chlorinated solvents. **d** Adjusted odds ratios with 95 % CI for interviewed ASD cases ($n = 217$) and controls ($n = 224$) associated with quartiles of exposure during pregnancy for other HAPs

exposure, after adjustment for covariates. PAHs and methylene chloride were of borderline significance ($p = 0.060$ and $p = 0.080$, respectively). Lead exposure, third quartile compared to first, was significant (OR = 1.54, 95 % CI = 1.00–2.38) as well as toluene (OR = 1.54, 95 % CI = 1.03–2.28) third to first quartile. There was a borderline significant effect for benzene (OR = 1.46, 95 % CI = 0.98–2.18) third quartile compared to first. Table 3 also shows the overall measure of metal compounds (arsenic, cadmium, chromium, mercury, manganese, nickel, and lead), aromatic solvents (benzene, ethyl benzene, styrene, toluene, and xylenes), and chlorinated solvents (methylene chloride, trichloroethane, perchloroethylene, and vinyl chloride), none of which were statistically significant in either analysis. For the aromatic solvents, the third compared to first quartile was borderline ($p = 0.064$).

The supplement (Additional file 1: Tables S2 and S3, Figures S1-S4) provides information on the sensitivity analysis of the singleton births. The interviewed control, singleton-only analysis again resulted in only styrene exposure remaining significantly associated with ASD status after adjustment for maternal education, race, age, smoking, child's year of birth, and child's sex. For the BC control, singleton-only analysis, exposure to arsenic, methylene chloride, PAHs, lead and cyanide reached statistical significance in addition to chromium and styrene. Although the confidence intervals for these additional suspect pollutants were wide in the interviewed control analysis, the odds ratios were elevated to a similar degree.

We noted a possible differential response rate for cases and BC controls in Armstrong and Beaver counties (see Table 1), with fewer cases in Beaver and fewer controls for Armstrong. We conducted a sensitivity analysis for the second BC control analysis, excluding Beaver and Armstrong County cases and controls, to determine if there would be any effect on the results of the analyses. We found similar results for chromium (OR = 1.60, 95 % CI = 1.04 -2.47) and for styrene (OR = 1.70, 95 % CI =

Table 3 Adjusted OR with 95 % CI for ASD associated with quartiles of exposure during pregnancy: interviewed cases ($n = 217$) and controls ($n = 224$) vs cases ($n = 215$) and birth certificate (BC) controls ($n = 4856$)[a]

Pollutant	Quartile (compared to 1)	Interviewed Control Adjusted				BC Control Adjusted			
		OR	Lower 95 % CI	Upper 95 % CI	p-value	OR	Lower 95 % CI	Upper 95 % CI	p-value
Metals									
Arsenic	2	1.23	0.69	2.20	0.477	1.36	0.89	2.07	0.154
	3	1.47	0.83	2.59	0.183	1.38	0.92	2.07	0.116
	4	1.28	0.71	2.28	0.415	1.33	0.87	2.02	0.183
Cadmium	2	1.07	0.61	1.86	0.817	1.17	0.79	1.73	0.443
	3	0.93	0.53	1.63	0.799	1.01	0.68	1.49	0.967
	4	0.93	0.53	1.64	0.804	1.15	0.78	1.70	0.466
Chromium	2	1.14	0.64	2.03	0.664	1.29	0.84	1.96	0.240
	3	1.14	0.64	2.03	0.651	1.28	0.85	1.95	0.240
	4	1.52	0.87	2.66	0.139	1.60	1.08	2.38	0.020
Mercury	2	0.64	0.36	1.11	0.112	0.79	0.54	1.17	0.250
	3	1.01	0.59	1.71	0.986	1.06	0.74	1.51	0.744
	4	0.60	0.34	1.06	0.079	0.75	0.51	1.13	0.169
Manganese	2	0.77	0.44	1.36	0.370	0.94	0.64	1.40	0.770
	3	0.75	0.43	1.32	0.321	0.92	0.62	1.36	0.665
	4	1.10	0.64	1.90	0.733	1.22	0.84	1.76	0.295
Nickel	2	0.87	0.51	1.50	0.622	1.08	0.74	1.56	0.700
	3	0.49	0.27	0.89	0.018	0.87	0.57	1.32	0.516
	4	0.76	0.44	1.31	0.317	0.93	0.65	1.35	0.718
Lead	2	1.33	0.77	2.32	0.311	1.41	0.96	2.08	0.080
	3	0.82	0.45	1.49	0.515	1.54	1.00	2.38	0.049
	4	1.10	0.63	1.94	0.734	1.33	0.90	1.97	0.158
Selenium	2	0.72	0.42	1.25	0.247	0.97	0.66	1.43	0.880
	3	0.93	0.54	1.58	0.776	1.21	0.85	1.74	0.292
	4	0.59	0.33	1.05	0.071	0.80	0.53	1.20	0.285
Aromatic Solvents									
Benzene	2	0.98	0.55	1.73	0.938	1.10	0.73	1.66	0.651
	3	1.12	0.64	1.95	0.690	1.46	0.98	2.18	0.059
	4	1.08	0.62	1.90	0.786	1.21	0.81	1.81	0.346
Ethyl benzene	2	0.92	0.52	1.62	0.763	1.15	0.76	1.74	0.498
	3	1.04	0.60	1.81	0.891	1.38	0.92	2.05	0.116
	4	1.16	0.66	2.03	0.609	1.23	0.84	1.82	0.291
Styrene	2	1.29	0.72	2.31	0.396	1.74	1.15	2.65	0.009
	3	1.09	0.60	1.98	0.784	1.11	0.71	1.75	0.648
	4	2.04	1.17	3.58	0.013	1.61	1.08	2.40	0.018
Toluene	2	0.97	0.55	1.70	0.914	1.26	0.84	1.90	0.262
	3	1.02	0.58	1.77	0.955	1.54	1.03	2.28	0.033
	4	0.98	0.55	1.72	0.930	1.20	0.80	1.79	0.376
Xylenes	2	0.76	0.42	1.36	0.352	1.12	0.73	1.73	0.593
	3	1.25	0.72	2.15	0.427	1.35	0.92	1.98	0.121
	4	1.04	0.59	1.83	0.895	1.23	0.83	1.83	0.310

Table 3 Adjusted OR with 95 % CI for ASD associated with quartiles of exposure during pregnancy: interviewed cases ($n = 217$) and controls ($n = 224$) vs cases ($n = 215$) and birth certificate (BC) controls ($n = 4856$)[a] *(Continued)*

Chlorinated Solvents									
Methylene chloride	2	1.02	0.58	1.78	0.958	1.13	0.75	1.71	0.548
	3	0.80	0.45	1.42	0.446	1.15	0.77	1.72	0.497
	4	1.07	0.61	1.85	0.822	1.41	0.96	2.07	0.082
Trichloroethane	2	1.25	0.71	2.21	0.447	1.16	0.77	1.75	0.485
	3	1.22	0.69	2.15	0.493	1.16	0.78	1.73	0.467
	4	1.22	0.68	2.17	0.509	1.23	0.82	1.85	0.323
Perchloroethylene	2	0.91	0.53	1.58	0.743	1.19	0.80	1.75	0.388
	3	0.93	0.53	1.62	0.791	1.14	0.76	1.71	0.530
	4	0.92	0.52	1.63	0.778	1.14	0.77	1.69	0.515
Trichloroethylene	2	1.00	0.57	1.76	0.996	1.23	0.81	1.85	0.331
	3	1.09	0.62	1.91	0.770	1.17	0.80	1.72	0.416
	4	1.04	0.59	1.84	0.902	1.18	0.79	1.76	0.423
Vinyl chloride	2	0.99	0.56	1.74	0.962	1.00	0.67	1.49	0.991
	3	1.02	0.58	1.79	0.950	1.03	0.68	1.56	0.879
	4	1.18	0.67	2.07	0.561	1.06	0.72	1.56	0.782
Other HAPs									
Hydrazine	2	0.71	0.42	1.17	0.178	0.62	0.28	1.39	0.248
	3	1.23	0.62	2.44	0.559	1.04	0.74	1.46	0.813
	4	0.82	0.47	1.44	0.492	1.23	0.83	1.84	0.304
PAHs	2	1.10	0.62	1.95	0.738	1.41	0.92	2.16	0.112
	3	1.01	0.57	1.79	0.973	1.27	0.85	1.90	0.251
	4	1.33	0.76	2.32	0.323	1.44	0.98	2.11	0.064
Diesel PM	2	1.15	0.66	2.00	0.634	1.38	0.93	2.06	0.112
	3	1.00	0.57	1.77	0.992	1.30	0.86	1.96	0.210
	4	1.04	0.59	1.84	0.887	1.25	0.83	1.87	0.282
Allyl chloride	2	0.75	0.41	1.34	0.328	1.13	0.75	1.71	0.548
	3	1.15	0.66	1.99	0.628	1.28	0.86	1.88	0.221
	4	1.26	0.73	2.17	0.405	1.17	0.80	1.70	0.424
Carbon disulfide	2	1.36	0.78	2.37	0.281	1.13	0.76	1.67	0.558
	3	0.79	0.44	1.45	0.451	0.82	0.53	1.27	0.371
	4	1.28	0.74	2.24	0.382	1.20	0.82	1.76	0.349
Cresols	2	0.86	0.49	1.53	0.611	1.12	0.74	1.69	0.591
	3	1.03	0.60	1.79	0.904	1.31	0.88	1.94	0.183
	4	1.05	0.60	1.85	0.854	1.18	0.79	1.76	0.424
Cumene	2	0.93	0.52	1.66	0.804	1.27	0.83	1.95	0.278
	3	1.43	0.82	2.48	0.205	1.33	0.91	1.93	0.143
	4	1.01	0.57	1.79	0.975	1.36	0.91	2.05	0.138
Cyanide	2	1.20	0.67	2.14	0.550	0.90	0.58	1.40	0.637
	3	1.42	0.81	2.49	0.218	1.17	0.80	1.71	0.430
	4	1.19	0.67	2.12	0.546	1.36	0.92	2.01	0.123
2,4-Dinitrotoluene	2	0.73	0.40	1.31	0.288	1.11	0.73	1.69	0.618
	3	1.18	0.68	2.03	0.566	1.35	0.92	1.98	0.130
	4	1.25	0.73	2.16	0.422	1.19	0.81	1.74	0.373

Table 3 Adjusted OR with 95 % CI for ASD associated with quartiles of exposure during pregnancy: interviewed cases ($n = 217$) and controls ($n = 224$) vs cases ($n = 215$) and birth certificate (BC) controls ($n = 4856$)[a] *(Continued)*

Ethylene Oxide	2	1.36	0.78	2.38	0.277	1.11	0.76	1.63	0.588
	3	1.13	0.64	2.00	0.686	1.08	0.72	1.62	0.710
	4	1.04	0.58	1.87	0.885	0.97	0.65	1.46	0.890
Hexane	2	0.90	0.51	1.60	0.718	1.23	0.82	1.85	0.313
	3	1.04	0.60	1.81	0.891	1.28	0.86	1.90	0.228
	4	1.12	0.64	1.96	0.689	1.27	0.86	1.87	0.239
Methanol	2	1.08	0.60	1.92	0.805	0.87	0.57	1.33	0.520
	3	1.31	0.74	2.29	0.353	1.21	0.82	1.79	0.328
	4	1.29	0.73	2.26	0.379	1.10	0.74	1.63	0.642
Index Scores									
Metals	2	0.69	0.39	1.23	0.209	0.96	0.65	1.42	0.842
	3	0.76	0.45	1.27	0.295	1.03	0.70	1.50	0.889
	4	0.93	0.53	1.63	0.790	1.17	0.80	1.70	0.423
Aromatic Solvents	2	0.81	0.47	1.40	0.447	1.17	0.79	1.73	0.446
	3	1.16	0.66	2.04	0.599	1.45	0.98	2.16	0.064
	4	1.10	0.63	1.93	0.745	1.20	0.81	1.78	0.368
Chlorinated Solvents	2	0.88	0.50	1.55	0.653	1.15	0.76	1.73	0.512
	3	1.00	0.58	1.73	1.000	1.10	0.75	1.62	0.609
	4	0.99	0.56	1.75	0.967	1.21	0.81	1.79	0.357

[a]All births, adjusted for mother's age, education, race, smoking, child's birth year (continuous), and child's sex

1.12–2.58). The remaining compounds were not statistically significant in either the original or the sensitivity analysis excluding Armstrong and Beaver, indicating very little effect on the overall results from the study population in these counties.

Shown in Table 4 are the adjusted odds ratios and 95 % CIs for ASD (fourth compared to first quartile) associated with exposure to individual NATA air toxics that were statistically significant in either the interviewed case–control or the BC case–control analysis of all births or in the sensitivity analysis of only the singleton births. Seven compounds were found to be related to ASD risk (arsenic, chromium, methylene chloride, PAHs, styrene, cyanide and lead). There is consistency in the adjusted odds ratios for NATA compounds when comparing the results from the two different control groups. The most notable difference in the two control groups is the wider confidence intervals for the first control due to its smaller sample size.

A backward stepwise multiple logistic regression analysis was conducted in order to consider the contribution of these seven compounds identified as "compounds of interest" while controlling for important covariates of mother's education, race, age, smoking, child's birth year and sex. For both the interviewed case–control and BC comparisons, only styrene remained in the final model of the seven air toxics, adjusting for covariates (fourth to first quartile, interviewed: OR = 2.04, 95 % CI = 1.17–3.58, $p = 0.013$; BC: OR = 1.61, 95 % CI = 1.08–2.40, $p = 0.018$).

Finally, a factor analysis using PCA and varimax rotation produced seven factors that explained almost 75 % of the variance of the original set of 30 air toxics. These factors appeared to represent pollution sources such as traffic, metal manufacturing, and plastic and rubber production. It is therefore possible that styrene or chromium, both individually associated with ASD risk in our study, are surrogates for related groups of agents. Future work will investigate methods to assess whether any of these groups of air toxics are associated with increased risk for ASD.

Discussion

Although this study was exploratory in nature, we targeted air toxics found to be associated with ASD in three previous epidemiology studies using NATA [17–19]. Of the twelve compounds found to be associated with ASD in these previous three investigations, five compounds (arsenic, lead, chromium, styrene and methylene chloride) were found to be statistically significant in at least one of our four sets of control comparisons (interviewed all births, BC all births, interviewed singletons, and BC singletons). Styrene was statistically significant across all four comparisons, and chromium was statistically significant for all births and singleton births within the BC control adjusted analyses. Of the

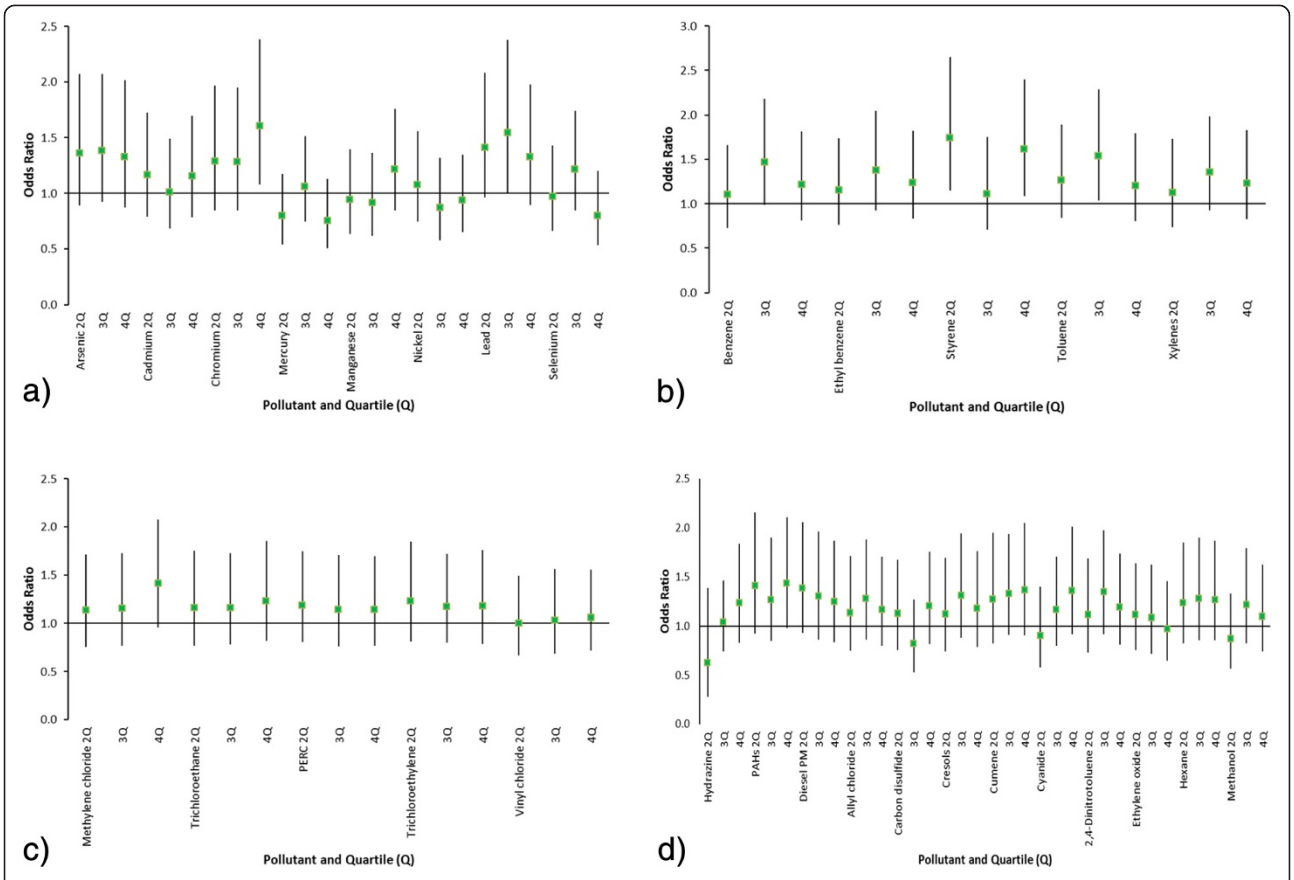


Fig. 2 **a** Adjusted odds ratios with 95 % CI for ASD cases ($n = 215$) and BC controls ($n = 4{,}856$) associated with quartiles of exposure during pregnancy for metals. **b** Adjusted odds ratios with 95 % CI for ASD cases ($n = 215$) and BC controls ($n = 4{,}856$) associated with quartiles of exposure during pregnancy for aromatic solvents. **c** Adjusted odds ratios with 95 % CI for ASD cases ($n = 215$) and BC controls ($n = 4{,}856$) associated with quartiles of exposure during pregnancy for chlorinated solvents. **d** Adjusted odds ratios with 95 % CI for ASD cases ($n = 215$) and BC controls ($n = 4{,}856$) associated with quartiles of exposure during pregnancy for other HAPs

remaining 18 compounds examined, four exhibited statistical significance for the fourth compared to the first quartile or the third compared to the first quartile in at least one of the analyses. PAHs and cyanide exhibited elevated odds ratios comparing the fourth to the first quartile of exposure, with confidence limits that did not include one in the singleton BC comparisons. In the singleton BC analysis, benzene and toluene also exhibited statistically significant ORs in comparisons of the third to the first quartile, and diesel PM for the second to the first quartile. The odds ratios for a number of other compounds we evaluated were also elevated, but the confidence intervals included one. There was consistency in the magnitude of the adjusted odds ratios for NATA

Table 4 Adjusted[a] OR (95 % CI) for ASD associated with exposure during pregnancy to NATA air toxics (fourth vs first quartile)

Pollutant	Interviewed (217 Cases and 224 Controls)		Birth Certificate (215 Cases and 4,856 Controls)	
	All Births	Singleton Births	All Births	Singleton Births
Arsenic	1.28 (0.71–2.28)	1.38 (0.75–2.52)	1.33 (0.87–2.02)	1.62 (1.03–2.54)**
Chromium	1.52 (0.87–2.66)	1.58 (0.88–2.81)	1.60 (1.08–2.38)**	1.65 (1.09–2.50)**
Methylene chloride	1.07 (0.61–1.85)	1.33 (0.74–2.36)	1.41 (0.96–2.07)*	1.63 (1.08–2.45)**
PAHs	1.33 (0.76–2.32)	1.56 (0.87–2.77)	1.44 (0.98–2.11)*	1.64 (1.09–2.46)**
Styrene	2.04 (1.17–3.58)**	2.23 (1.24–4.00)**	1.61 (1.08–2.40)**	1.67 (1.09–2.54)**
Lead	1.10 (0.63–1.94)	1.21 (0.67–2.18)	1.33 (0.90–1.97)	1.52 (1.00–2.30)**
Cyanide	1.19 (0.67–2.12)	1.32 (0.73–2.36)	1.36 (0.92–2.01)	1.52 (1.01–2.30)**

[a]Models adjusted for maternal smoking, age, education, race, child's birth year, and sex of the child
**Significant (p-value < 0.05) *$p < .10$

compounds when comparing the results based on the two different control groups within our study for the seven compounds found to be related to ASD risk (arsenic, chromium, methylene chloride, styrene, lead, cyanide and PAHs). The most notable difference in the two control groups is the wider confidence interval for the first control due to its smaller sample size resulting in lower power to detect small differences. Styrene and chromium showed the strongest estimates of risk for both case–control comparisons with a range of odds ratios of 1.61–2.23 for styrene and 1.52–1.65 for chromium in the four sets of case–control comparisons.

This study used a semi-ecological design. Personal risk factors were obtained at the individual level, but exposure to the air toxics was assessed at the group level (census tract level). Also, we applied the NATA concentration estimates for 2005 to the full time period of this study, and they may not have been representative of exposures for other years. In the interviewed analysis, although we had information on changes in residential addresses in the prenatal and postnatal period, we did not have explicit mobility patterns for the mother-child pairs outside of these residential census tracts.

Each control group analysis had its unique strengths and weaknesses. We were able to conduct maternal interviews for cases and for the first control group to obtain full residential history information, thereby decreasing exposure misclassification bias. We were also able to examine the association between ASD and estimated exposure to NATA air toxics not only during pregnancy, but also for the first and second years of life—the first study to do so. The second control group, because it was a random sample representative of all births in the six county area (weighted 4:1 male:female), removed the issue of response bias among the controls. However, a limitation of the second set of case–control analyses was the inability to capture residences during pregnancy other than the address reported at the time of birth. We noted that 16.1 % of the case mothers and 12.9 % of the interviewed control mothers reported moving to a new address during the year before the infant's birth. Based on the sociodemographic characteristics of the birth certificate controls, the percentage that moved during pregnancy may have been even higher among the birth certificate controls, leading to exposure misclassification for the second set of control analyses.

Of the four studies (including ours) that used NATA to assess the risk of ASD associated with air toxics, the Windham et al. and Kalkbrenner et al. studies are the most similar with regard to case selection, and the use of birth certificates for residence and covariates. They identified cases using an existing surveillance system for California [19] and North Carolina and West Virginia [17]. Cases of ASD were identified as diagnosed through age 8. Windham et al. matched 284 cases by sex and month of birth to 657 controls from the same area randomly selected from the California birth–infant death certificate file; whereas Kalkbrenner et al. identified 383 children with ASD and 2,829 control children with speech and language impairment. Both used NATA chemicals from the 1996 HAP database as potential risk factors for ASD, which were assigned by census tract of the birth residence. In Windham's investigation, because concentrations of many of the chemicals were highly correlated, chemicals were combined into mechanistic and structural groups calculating summary index scores. The adjusted odds ratios (AORS) were elevated by 50 % in the top quartile of chlorinated solvents (95 % CI = 1.08–2.23) (methylene chloride, trichloroethylene, and vinyl chloride) and heavy metals (95 % CI = 1.05 to 2.12) (nickel, cadmium and mercury) compared to the combined lower two quartiles in cases compared to controls [19]. Kalkbrenner et al. calculated odds ratios corresponding to the odds of ASD for high pollutant concentrations (80^{th} percentile) compared to low pollutant concentrations (20^{th} percentile). Hazardous air pollutants with more precise and elevated OR estimates included methylene chloride, quinoline and styrene, with odds ratios that were between 1.4 and 1.8 [17]. Results of these two studies suggested a potential association between ASD and metals and possibly solvents.

Our interviewed case–control group was most like the Roberts et al. investigation as neither study utilized a surveillance system to identify ASD cases and both relied on personal interview for residential history of the mother during pregnancy and afterwards and other potential risk factors. Roberts et al. was able to identify the offspring of mothers who participated in the Nurses' Health Study II between 1987 and 2002 diagnosed with ASD [18]. Roberts et al. compared a total of 325 ASD cases to 22,098 controls from the same birth cohort matched on age and gender. Although ASD diagnosis was not confirmed, the authors did administer a diagnostic test by telephone to a randomly selected subset, and the medical background of the participants most likely adds strength to the accuracy of the diagnosis. We obtained diagnostic test results from the psychologist or health care provider of record. Roberts et al., comparing the highest quintile of exposure to the lowest for both sexes, found significant associations between ASD and exposure to overall metals (OR = 1.6, 95 % CI = 1.1–2.4), lead (OR = 1.6, 95 % CI = 1.1–2.3), manganese (OR = 1.5, 95 % CI = 1.1–2.2), mercury (OR = 1.4, 95 % CI = 0.9–

2.0), nickel (OR = 1.7, 95 % CI = 1.1–2.5) and methylene chloride (OR = 1.5, 95 % CI = 1.0–2.1). Other HAPS that reached significance in the highest quintile were cadmium and diesel PM. They adjusted for possible confounding factors including socioeconomic level, census tract level SES measures, maternal age, and year of birth [18].

Our second control was similar to Windham's investigation because residence and personal risk factors were obtained from the birth certificate in both studies. In general, the four NATA studies noted increased risk of ASD for certain heavy metals, chlorinated solvents (methylene chloride) and specific aromatic solvents (styrene).

Each previous NATA study investigated a different geographical area and used NATA assessments from varying years. Windham et al. and Kalkbrenner et al. used the 1996 NATA assessment, while our present study used the most recent NATA data available (2005). Roberts assigned exposure using the assessment closest to each year of birth, so all assessments from 1990 to 2002 were included. The US EPA advises that NATA results from different years should not be compared since there are changes in the methodology and emissions or source inputs for each assessment [20].

Nevertheless, we compiled the results for 13 NATA compounds for cases and controls from each of the major NATA/autism studies [17–19] for comparison purposes (see Additional file 1: Table S4). In general, the means and standard deviations in the Windham study using 1996 NATA reflect higher estimates of exposure for 9 of the 13 compounds. These levels were higher than those in our study for many of the metals (chromium, lead, mercury, and nickel), as well as for benzene, diesel PM, methylene chloride, styrene, and trichloroethylene. It should be noted that Windham's population was from the San Francisco Bay area, which is also highly urban and industrial and reflects air toxics modeled for 1996. In our study (SW PA), the arsenic and cadmium mean levels were higher compared to the other three studies. With respect to styrene, which was significantly associated with ASD in our study using either control group, the levels in the four studies ranked (from highest to lowest): Windham et al. (100 ng/m^3 cases, 90 ng/m^3 controls), Roberts et al. (60 ng/m^3), our present study (39 ng/m^3 cases, 38 ng/m^3 controls), and Kalkbrenner et al. (23 ng/m^3 North Carolina, 10 ng/m^3 West Virginia). The exposures for the West Virginia participants in the Kalkbrenner study tended to be the lowest, most likely because West Virginia is more rural compared to the regions considered in the other investigations. Both Roberts and Kalkbrenner found relationships with ASD and styrene exposure. Styrene was not entered as an individual pollutant in any of Windham's models.

Current research points to a variety of cellular, molecular and inflammatory pathways that directly damage brain structure or lead to a predisposition for disease that affects the CNS system through neuroinflammation, oxidative stress and glial activation [23, 24]. Diodovich et al. noted that styrene has been shown to cross the placenta. Animal studies clearly support the role of styrene in promoting cell proliferation and cell cycle progression as potentially favoring alterations in gene expression [25].

Styrene emissions come from a variety of sources, including point sources (e.g. plastic manufacturing, hazardous waste treatment, paint and coating manufacturing, and organic chemical manufacturing facilities) and on-road sources such as car exhaust [26, 27]. According to NATA 2005 county-level estimates, 4–30 % of styrene emissions across our six county study area were attributed to point sources. Non-point sources contributed 13–77 %, and on-road sources contributed 14–49 %. Other possible sources of styrene include occupational exposures and cigarette smoke [28]. Maternal smoking was considered in our analysis.

Chromium is also emitted from a variety of sources, processes, and industries, such as coal and oil combustion, electroplating, leather tanning, cement-producing plants, tobacco smoke, and the metal and textile industries [29]. Chromium is an additive in steel production as a hardener and a primary component of stainless steel. In our study area, point sources contributed 50–83 % of chromium emissions, non-point sources 7–22 %, and mobile sources <1 %.

Conclusions

Results of this case–control study in Southwestern Pennsylvania suggest that living in areas with higher ambient levels of styrene and chromium is associated with increased risk of ASD; moreover, there are borderline effects for PAHs and methylene chloride. When considering singleton births only, there were additional significant associations with arsenic, lead and cyanide. Our study was unique in that we were able to utilize two different kinds of control group analyses: the first using personal interviews capturing the period of pregnancy to age two, and the second a random sample of all births (weighted by sex) from the same time period based on birth certificate information. Our dataset enabled us to adjust for other suspected risk factors of ASD (age of mother, smoking history, maternal education, and race).

The above compounds represent air toxics of interest which require greater scrutiny to determine individual risk beyond the census tract or group level. Ground level monitoring of these targeted compounds should be conducted for multiple time periods (days of week and hours of the day) at multiple locations, including around major industrial sources. Future work should also

include time activity patterns to obtain spatiotemporal estimates of exposure to air toxics, taking into account the dynamic movement of individuals during daily life. In addition, a national or statewide autism registry would enhance access to a greater proportion of all ASD cases and enable greater participation into future research.

Additional file

Additional file 1: Recruitment flowcharts and results of the singleton only analysis. (DOCX 294 kb)

Abbreviations

BC: Birth certificate; CI: Confidence interval; GIS: Geographic information system; NATA: National Air Toxics Assessment; OR: Odds ratio; PM: Particulate matter.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EOT developed the design of the study and methodology, developed the data collection instrument, participated in all facets of the identification and recruitment of cases and controls and lead the analysis and write-up of the study findings. LPM carried out geocoding of the second control group, assignment of exposures and analysis. She also assisted in manuscript preparation. JRR participated in the design of the study, protocol development, questionnaire design, selection of birth certificate control group, geocoding of the cases and controls, data management and analysis of the case–control study. She also assisted in editing and final disposition of the manuscript. VCA was the statistician for the project. He developed the algorithm that assigned air toxic exposures to the ASD cases and controls to obtain prenatal, and postnatal period specific exposures based on residence. VCA interpreted these results. RKS, a geospatial information specialist provided expertise to JRR and LPM in linkage of the data at the resident specific level of the air toxics information and related analysis. Finally, SLS carried out analysis under the direction of JRR, EOT and VCA and contributed immeasurably to the final editing and completion of the manuscript. All authors have read and approved this manuscript.

Acknowledgements

We would like to thank Dr. Gayle Windham for her support and advisement during the early stages of the project and Dr. LuAnn Brink for her work with the air toxics database.

Author details

[1]Department of Epidemiology, University of Pittsburgh, Graduate School of Public Health, 130 DeSoto Street, A526 Crabtree, Pittsburgh, PA 15261, USA. [2]Department of Biostatistics, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA. [3]Department of Behavioral and Community Health Scienc, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA. [4]Department of Environmental and Occupational Health, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA.

Received: 2 March 2015 Accepted: 11 September 2015
Published online: 06 October 2015

References

1. CDC (Centers for Disease Control). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. Morbidity and Mortality Weekly Report Surveillance Summaries. 2014;63(SS02):1–21.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. Washington: 2000.
3. Karst JS, Van Hecke AV. Parent and Family Impact of Autism Spectrum Disorders: A Review and Proposed Model for Intervention Evaluation. Clinical Child and Family Psychology Review. 2012;15(3):247–77.
4. Institute of Medicine , Forum on Neuroscience and Nervous System Disorders. Autism and the Environment: Challenges and Opportunities for Research. Washingotn DC, 20001: Workshop Proceedings, National Academy Press; 2008. p. 358. ISBN:0-309-10882-9, (www.nap.edu) (http://napp.edu/catalog/11946.html).
5. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch Pediatr Adolesc Med. 2007;161(4):326–33.
6. Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, Levy SE, et al. The epidemiology of autism spectrum disorders. Annu Rev Public Health. 2007;28:235–58.
7. Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental Chemical Exposures and Autism Spectrum Disorders: A Review of the Epidemiological Evidence. Curr Probl Pediatr Adolesc Health Care. 2014;44(10):277–318.
8. Palmer RF, Blanchard S, Stein Z, Mandell D, Miller C. Environmental mercury release, special education rates, and autism disorder: an ecological study of Texas. Health Place. 2006;12(2):203–9.
9. Palmer RF, Blanchard S, Wood R. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. Health Place. 2009;15(1):18–24.
10. Roberts EM, English PB, Grether JK, Windham GC, Somberg L, Wolff C. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. Environ Health Perspect. 2007;115(10):1482–9.
11. Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Ritz B, et al. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. Environ Health Perspect. 2014;122(10):1103–9.
12. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential proximity to freeways and autism in the CHARGE study. Environmental Health Perspectives. 2011;119(6):873–7.
13. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic related air pollution, particulate matter, and autism. JAMA Psychiatry. 2013;70(1):71–7.
14. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient air pollution and autism in Los Angeles County, California. Children's Health. 2013;121(3):380–6.
15. Kalkbrenner AE, Windham GC, Serre ML, Akita Y, Wang X, Hoffman K, et al. Particulate Matter Exposure, Prenatal and Postnatal Windows of Susceptibility, and Autism Spectrum Disorders. Epidemiology. 2015;26(1):30–42.
16. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested-Case-Control Analysis within the Nurses' Health Study II Cohort. Environmental Health Perspectives. 2014. doi:10.1289/ehp.1408133.
17. Kalkbrenner AE, Daniels JL, Chen JC, Poole C, Emch M, Morrissey J. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology. 2010;20(7):615–24.
18. Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, et al. Perinatal air pollutant exposures and autism spectrum disorder in the children of nurses' health study II participants. Environ Health Perspect. 2013;121(8):978–84.
19. Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. Environ Health Perspect. 2006;114(9):1438–44.
20. EPA (Environmental Protection Agency). Technology Transfer Network Air Toxics 2005 National-Scale Air Toxics Assessment. http://www.epa.gov/ttn/atw/nata2005/tables.html (2005). Accessed 16 April 2014.
21. Von Ehrenstein OS, Aralis H, Cockburn M, Ritz B. In Utero Exposure to Toxic Air Pollutants and Risk of Childhood Autism. Epidemiology. 2014;25(6):851–8.
22. Pennsylvania Department of Health. Birth Statistics. http://www.portal.state.pa.us/portal/server.pt?open=514&objID=809799&mode=2. Accessed 10 June 2015.
23. Block ML, Calderón-Garcidueñas L. Air pollution: Mechanisms of neuroinflammation & CNS Disease. Trends Neurosci. 2009;32(9):506–16.
24. Genc S, Zadeoglulari Z, Fuss SH, Genc K. The adverse effects of air pollution on the nervous system. Journal of Toxicology. 2012. doi:10.1155/2012/782462.
25. Diodovich C, Bianchi MG, Bowe G, Acquati F, Taramelli R, Parent-Massin D, et al. Response of human cord blood cells to styrene exposure: evaluation of its effects on apoptosis and gene expression by genomic technology. Toxicology. 2004;200:145–57.

26. National Toxicology Program. U.S. Department of Health and Human Services. Center for the Evaluation of Risks to Human Reproduction. Monograph on the Potential Human Reproductive and Developmental Effects of Styrene. http://ntp.niehs.nih.gov/ntp/ohat/styrene/styrene_monograph.pdf (2006). Accessed 30 October 2014.
27. Wang J, Jin L, Gao J, Shi J, Zhao Y, Liu S, et al. Investigation of speciated VOC in gasoline vehicular exhaust under ECE and EUDC test cycles. Science of the Total Environment. 2013;445-446:110–6.
28. Cohen JT, Carlson G, Charnley G, Coggon D, Delzell E, Graham JD, et al. A comprehensive evaluation of the potential health risks associated with occupational and environmental exposure to styrene. J Toxicol Environ Health B Crit Rev. 2002;5:1–265.
29. ATSDR (Agency for Toxic Substances & Disease Registry). Chromium Toxicity. http://www.atsdr.cdc.gov/csem/csem.asp?csem=10&po=5 (2014). Accessed 16 December 2014.

DeFranco et al. Environmental Health (2016) 15:6
DOI 10.1186/s12940-016-0094-3

Environmental Health

RESEARCH Open Access

Exposure to airborne particulate matter during pregnancy is associated with preterm birth: a population-based cohort study

Emily DeFranco[1,2*], William Moravec[2], Fan Xu[3], Eric Hall[1], Monir Hossain[4], Erin N. Haynes[3], Louis Muglia[1,2] and Aimin Chen[3]

Abstract

Background: Test the hypothesis that exposure to fine particulate matter in the air ($PM_{2.5}$) is associated with increased risk of preterm birth (PTB).

Methods: Geo-spatial population-based cohort study using live birth records from Ohio (2007–2010) linked to average daily measures of $PM_{2.5}$, recorded by 57 EPA network monitoring stations across the state. Geographic coordinates of the home residence for births were linked to the nearest monitoring station using ArcGIS. Association between PTB and high $PM_{2.5}$ levels (above the EPA annual standard of 15 μg/m^3) was estimated using GEE, with adjustment for age, race, education, parity, insurance, tobacco, birth season and year, and infant gender. An exchangeable correlation matrix for the monitor stations was used in the models. Analyses were limited to non-anomalous singleton births at 20-42weeks with no known chromosome abnormality occurring within 10 km of a monitor station.

Results: The frequency of PTB was 8.5 % in the study cohort of 224,921 singleton live births. High $PM_{2.5}$ exposure (>EPA recommended maximum) occurred frequently during the study period, with 24,662 women (11 %) having high exposure in all three trimesters. Pregnancies with high $PM_{2.5}$ exposure through pregnancy had increased PTB risk even after adjustment for coexisting risk factors, adjOR 1.19 (95 % CI 1.09–1.30). Assessed per trimester, high 3rd trimester $PM_{2.5}$ exposure resulted in the highest PTB risk, adjOR 1.28 (95 % CI 1.20–1.37).

Conclusions: Exposure to high levels of particulate air pollution, $PM_{2.5}$, in pregnancy is associated with a 19 % increased risk of PTB; with greatest risk with high 3rd trimester exposure. Although the risk increase associated with high $PM_{2.5}$ levels is modest, the potential impact on overall PTB rates is robust as all pregnant women are potentially at risk. This exposure may in part contribute to the higher preterm birth rates in Ohio compared to other states in the US, especially in urban areas.

Keywords: Air pollution, Particulate matter, PTB, Preterm birth, Prematurity

* Correspondence: emily.defranco@uc.edu
[1]Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[2]Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, MSB Room 4553B, Cincinnati, OH 45267-0526, USA
Full list of author information is available at the end of the article

Background

Since the industrial revolution, it has become increasingly evident that environmental toxicants contribute to human disease. Air pollution is associated with several acute and chronic cardiopulmonary diseases. Particulate air pollution, in particular, has been found to be harmful in numerous studies, and was 9th leading risk factor in the 2010 Global Burden of Disease Study [1]. Particulate air pollution is a heterogeneous group of airborne matter that ranges in size from a few hundredths of a micrometer to visible particles up to 100 μm. Combustion is the main source of harmful particulate matter (PM). Fine particulate matter ($PM_{2.5}$, referring to the upper limit of this fraction being 2.5 μm) has received much research and regulatory attention. As opposed to ultrafine particles – which are stable for only a short period of time, and coarse particles – whose travel is generally limited by the large size of the particles, $PM_{2.5}$ can be both stable for long periods of time and are small enough to be distributed far from their source. $PM_{2.5}$ comprises particles composed of hydrocarbons, organic compounds, ultrafine particle aggregates, biologic endotoxins, metals, and ions. Short-term exposure to $PM_{2.5}$ can cause premature death, especially from cardiac and pulmonary disease. Long-term exposure to $PM_{2.5}$ can also cause premature death from cardiac and pulmonary disease, but can also reduce lung development and lead to chronic respiratory diseases in children [2]. The EPA does monitor and set regulations for safe $PM_{2.5}$ levels (www.epa.gov/ttn/naaqs/).

The connections between maternal toxin exposures and adverse birth outcomes is an emerging field of study that has begun to show that environmental toxicants are likely to be associated with some poor birth outcomes including stillbirth, low birthweight, some congenital anomalies, and preterm birth [3].

Several prior studies have reported the association between air pollutants and preterm birth, but report inconsistent findings of the association between preterm birth and increased $PM_{2.5}$ levels [4–13]. Previous studies have been limited in design by exposures with measures at a single time point or with a lack of thorough adjustment for important clinical or socio-demographic risk factors. In this study we aim to integrate air quality measures from statewide monitoring stations with vital records to perform geospatial analyses testing the hypothesis that exposure to fine particles in the air ($PM_{2.5}$) is associated with preterm birth risk.

Methods

The Ohio Department of Health and Human Subjects Institutional Review Board approved a protocol for this study. This study was exempt from review by the Institutional Review Board at the University of Cincinnati, Cincinnati, Ohio. A data set generated from vital records of all live births that occurred in the state from 2007–2010 was provided for this analysis by the Ohio Department of Health, $n = 597{,}000$.

This is a geo-spatial population-based cohort study. The primary exposure was high level of airborne $PM_{2.5}$, fine particulate matter in the air measuring <2.5 μm in diameter. Trimester-specific and total pregnancy average daily $PM_{2.5}$ levels were categorized as high exposure if the average over the specified time period was greater than 15 $\mu g/m^3$, which was the EPA annual standard during the period of study. A secondary analysis was then performed modeling $PM_{2.5}$ levels as a continuous variable. The primary outcome was preterm birth was defined as delivery prior to 37 completed weeks of gestation. Gestational age was defined by the best obstetric estimate variable in the birth record, which combines last menstrual period and ultrasound parameters, as is commonly accepted in clinical practice for gestational age estimation. Analyses were limited to non-anomalous singleton live births.

Daily measures of $PM_{2.5}$, recorded by 57 monitoring stations across the state of Ohio, were obtained from the Environmental Protection Agency from 2007–2010 and monthly averages were calculated for each station [14]. Maternal address at time of birth was geocoded and distance to the nearest EPA monitoring station was calculated using ArcGIS 10.1 (ESRI, Redlands, CA) software. Births at gestational ages 20 to 42 weeks with a maternal home address within 10 km of an EPA $PM_{2.5}$ monitoring station were included in this analysis ($n = 224{,}921$, Fig. 1). Average monthly $PM_{2.5}$ levels from the nearest EPA station were linked to the birth record data. Average $PM_{2.5}$ levels for each trimester and an average for the entire pregnancy were calculated for each birth included in this analysis.

Demographic, medical and delivery characteristics of preterm live births (<37 weeks) were compared to term live births (37–42 weeks) using t-test for continuous variable comparisons and χ^2 tests for categorical variables. The association between preterm birth and high $PM_{2.5}$ exposure was estimated using generalized estimating equations (GEE), with adjustment for the confounding influences of age, race, education, parity, insurance, tobacco, birth season and year, and infant sex. Odds ratios for high $PM_{2.5}$ exposure during the first, second, and third trimester as well as high exposure averaged over the entire pregnancy were estimated from separate models with adjustment for all factors listed above. Covariates include in the models were chosen based on significant differences noted among bivariate comparisons, biologic plausibility, and parsimony within the model.

An exchangeable correlation matrix for the monitoring stations was used in the GEE models to account for

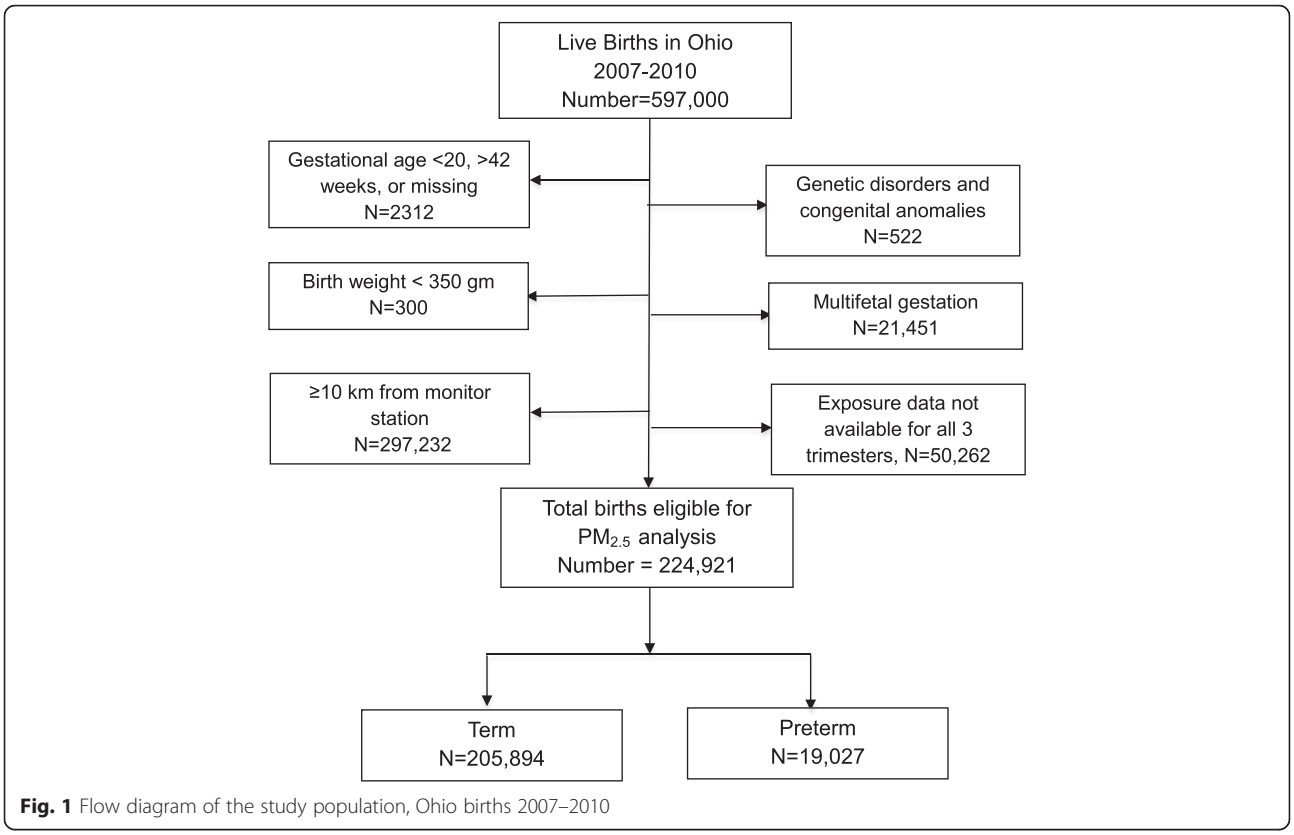


Fig. 1 Flow diagram of the study population, Ohio births 2007–2010

spatial correlation within the same $PM_{2.5}$ monitor. Analyses were performed using SAS version 9.3, SAS Institute Inc., Cary, NC, USA. Comparisons with a probability value <0.05 or 95 % confidence interval without inclusion of the null were considered statistically significant. Population attributable risk percentage (PAR%) was calculated as: $PAR\% = 100 \times Pe\ (RR - 1)/(Pe(RR-1) + 1)$, where Pe is percentage of high exposure in the entire population (approximately 10 % for the population included in this study) and RR is relative risk. Odds ratios approximate the relative risk in studies with an outcome rate of less than 10 %, as in this study. Therefore we utilized estimated odds ratios in lieu of relative risk in the PAR calculation. The PAR calculation inherently assumes a causal relationship, which is yet unproven in the association of particulate matter and preterm birth. With this in mind, we provide this calculation in effort to estimate the potential contribution of high $PM_{2.5}$ exposure to preterm birth on a population level.

Results

The study population included 224,921 singleton non-anomalous live births: 19,027 preterm births and 205,894 term births, Fig. 1. The preterm rate decreased during the study period, from 8.6 % in 2007 to 8.2 % in 2010, Table 1. Most births analyzed (97 %) occurred in very urban areas, where most monitoring stations are located and exposure levels are likely to be highest. Preterm birth rates were higher among the oldest mothers, age ≥40 years, 10.9 %, and non-Hispanic black mothers, 11.2 %, as well as women with lower education level and tobacco use. Women with no prenatal care had the highest rate of singleton preterm birth, 19.8 %. Season of conception had no influence on preterm birth rate.

The locations of $PM_{2.5}$ monitor stations in Ohio and preterm births during the study period are demonstrated in Fig. 2. The mean $PM_{2.5}$ level during the study period (2007–2010) in Ohio was 13.03 $\mu g/m^3$ [±1.57 $\mu g/m^3$, IQR (Q1: 11.84, Q3: 14.13, IQR: 2.3)], which is higher than the current US EPA National Ambient Air Quality Standard (NAAQS) of 12 $\mu g/m^3$. Mean $PM_{2.5}$ level, IQR for the entire cohort per trimester was: 1^{st} trimester 13.19, 2.36 $\mu g/m^3$; 2^{nd} trimester 12.98, 2.08 $\mu g/m^3$; 3^{rd} trimester 12.93, 2.30 $\mu g/m^3$.

The frequency of high exposure to $PM_{2.5}$ greater than the EPA standard of 15 $\mu g/m^3$ ranged from 17 to 20 % for each trimester of pregnancy, and 11 % of parturients had high exposure throughout pregnancy in all three trimesters. The frequency of high $PM_{2.5}$ exposure was higher in preterm births compared to term births, see Table 2. The preterm birth rate was also increased with high $PM_{2.5}$ exposure during the first and third trimester, and when there was high $PM_{2.5}$ exposure averaged over the entire pregnancy, as demonstrated in Table 3.

Table 1 Maternal Characteristics, Ohio 2007–2010

	Preterm (%) $N = 19,027$	Term (%) $N = 205,894$	*p*-value	Total births (%) $N = 224,921$
Demographic factors				
Advanced maternal age				
35 – 39 years	1901 (10.0)	19,302 (9.4)	<0.01	21,203 (9.4)
≥40 years	482 (2.5)	3952 (1.9)		4434 (2.0)
Race and ethnicity				
Non-Hispanic White	9940 (52.7)	127,636 (62.6)	<0.01	137,576 (61.2)
Non-Hispanic Black	7507 (39.8)	59,630 (29.2)		67,137 (30.1)
Hispanic	937 (5.0)	10,583 (5.2)		11,520 (5.2)
Other	457 (2.4)	6.116 (3.0)		6573 (2.9)
Social behaviors & socioeconomic factors				
Education				
Less than high school	4778 (25.4)	40,658 (19.9)	<0.01	45,436 (20.4)
High school graduate	5127 (27.3)	50,721 (24.9)		55,848 (25.1)
Some postsecondary	8875 (47.3)	112,590 (55.2)		121,465 (54.5)
Tobacco use	4568 (24.0)	38,292 (18.6)	<0.01	42,860 (19.1)
Medicaid insurance	9672 (50.8)	87,631 (42.6)	<0.01	97,303 (43.3)
Prenatal care initiation				
First trimester	8051 (61.6)	103,232 (67.7)	<0.01	111,283 (67.2)
Second trimester	3219 (24.6)	36,882 (24.2)		40,101 (24.2)
Third trimester	708 (5.4)	7897 (5.2)		8605 (5.2)
No prenatal care	1092 (8.4)	4422 (2.9)		5514 (3.3)
Year of birth				
2007	5234 (27.5)	55,325 (26.9)	0.01	60,559 (26.9)
2008	4969 (26.1)	52,708 (25.6)		57,677 (25.6)
2009	4600 (24.2)	50,364 (24.5)		54,964 (24.4)
2010	4225 (22.2)	47,497 (23.1)		51,721 (23.0)
Season				
Winter	4755 (25.0)	50,205 (24.4)	0.26	54,960 (24.4)
Spring	4787 (25.1)	51,827 (25.2)		56,614 (25.2)
Summer	4835 (25.4)	53,173 (25.8)		58,008 (25.8)
Fall	4650 (24.4)	50,689 (24.6)		55,339 (24.6)

Dichotomous variables for first 2 columns are presented as percent of total for each characteristic
Continuous variables are presented as median (IQR) for non-normally distributed data and mean +/- standard deviation for normally distributed data

Likewise, the mean $PM_{2.5}$ levels during each trimester when compared between term and preterm pregnancies demonstrated significantly higher average $PM_{2.5}$ levels during the first and third trimester for the preterm birth group compared to term births, $p = 0.01$ (data not displayed in table). Likewise, the overall pregnancy average $PM_{2.5}$ levels were higher for the preterm birth group compared to the term birth group, $p < 0.01$.

Logistic regression models were constructed to identify factors associated with preterm birth. Factors with significant associations included maternal age > 35, non-Hispanic black race, Hispanic ethnicity, high school education or less, no prenatal care, tobacco use, high $PM_{2.5}$ exposure during the third trimester, and high $PM_{2.5}$ exposure over the entire pregnancy (Table 4 and Fig. 3). High $PM_{2.5}$ levels > 15 μg/m^3 during the third trimester or high when averaged over the entire pregnancy were associated with an increased risk of preterm birth <37 weeks of gestation, adjOR 1.28 (CI 1.20, 1.37) and adjOR 1.19 (CI 1.09, 1.30), respectively (Table 4). When $PM_{2.5}$ exposure was modeled as a continuous variable in a secondary analysis, no significant association between exposure and preterm birth was

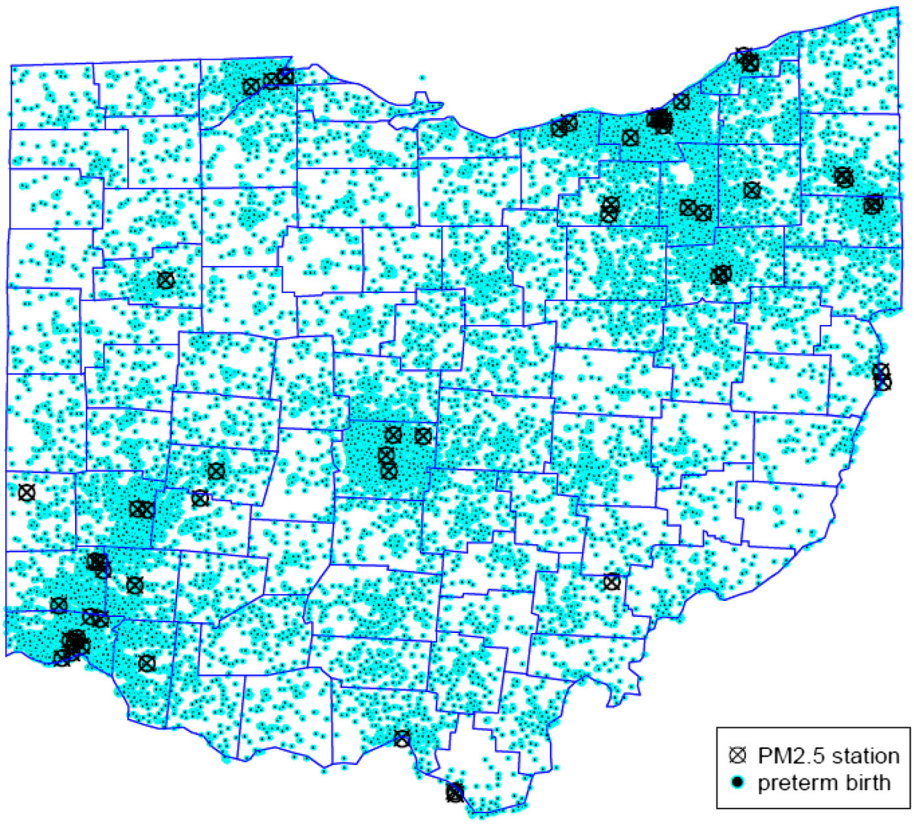


Fig. 2 Preterm births and $PM_{2.5}$ monitoring stations in Ohio, 2007–2010

observed: adjOR 0.99 (CI 0.98, 1.00) for first trimester, adjOR 0.98 (CI 0.97, 1.00) second trimester, adjOR 1.0 (CI 0.99, 1.00) third trimester, and pregnancy average adjOR 0.98 (CI 0.96, 1.0).

The attributable risk of preterm birth related to high $PM_{2.5}$ exposure > 15 μg/m^3 was 0.0172 (95 % CI 0.0135 – 0.0208). The attributable risk percent: (Ie-Iu)/Ie is 17.18 (13.49 – 20.86) %, i.e. for the exposed population, 17.18 % of preterm births were from high $PM_{2.5}$ exposure. In our study sample in which 10.96 % of the population was exposed to high $PM_{2.5}$, the population attributable risk percentage of high $PM_{2.5}$ exposure was 2.22 % for preterm birth.

Discussion

Our study adds to the growing body of evidence that particulate matter in the air is deleterious to human health. In our study sample, exposure to high levels of $PM_{2.5}$ > 15 μg/m^3 was significantly associated with preterm birth – both when high exposure occurred on average over the course of pregnancy and with high exposure limited to just the third trimester. Our calculated attributable risk percent estimates that decreasing $PM_{2.5}$ levels below this EPA standard threshold could theoretically decrease preterm birth by 17.18 % in the exposed group, corresponding to a 2.22 % decrease in preterm birth rate in the population.

Table 2 $PM_{2.5}$ levels in Ohio 2007 – 2010, by trimester of exposure in pregnancy and preterm status

	Preterm births $N = 19{,}027$	Term births $N = 205{,}894$		All live births $N = 224{,}921$
	% $PM_{2.5} \geq 15$ μg/m^3	% $PM_{2.5} \geq 15$ μg/m^3	*p*-value	% $PM_{2.5} \geq 15$ μg/m^3
First trimester	22.97	21.81	<0.001	21.91
Second trimester	17.30	17.36	0.835	17.36
Third trimester	22.84	18.90	<0.001	19.23
Entire pregnancy	12.94	10.78	<0.001	10.96

% $PM_{2.5} \geq 15$ μg/m^3 = percent of births in Ohio with average exposure level exceeding the EPA standard of 15 μg/m^3

Table 3 Preterm birth rate by $PM_{2.5}$ levels in Ohio 2007 – 2010 and trimester of exposure in pregnancy

	$PM_{2.5} < 15$ μg/m^3		$PM_{2.5} \geq 15$ μg/m^3		
	n	% Preterm	n	% Preterm	*p*-value
First trimester	175,649	8.34	49,272	8.87	<0.001
Second trimester	185,883	8.47	39,038	8.43	0.835
Third trimester	181,665	8.08	43,256	10.05	<0.001
Entire pregnancy	200,259	8.27	24,662	9.99	<0.001

% preterm represents the rate of birth <37 weeks of gestational age among the study cohort of singleton non-anomalous live births

Table 4 Logistic regression of factors associated with preterm birth, Ohio 2007-2010

	Adjusted odds ratio[2]	95 % confidence interval
Maternal age, years		
<20	0.93	0.84, 1.02
20–24	0.99	0.94, 1.05
25–29	1.00	Referent
30–34	1.04	0.97, 1.10
35–39	1.27	1.19, 1.36
≥40	1.52	1.37, 1.69
Maternal race		
Non-Hispanic white	1.00	Referent
Non-Hispanic black	1.46	1.36, 1.57
Hispanic	1.10	1.01, 1.18
Other Non-Hispanic	1.02	0.88, 1.18
Maternal education level		
Less than high school	1.13	1.07, 1.19
High school only	1.23	1.17, 1.29
Postsecondary education	1.00	Referent
Prenatal care initiation		
First trimester	1.00	Referent
Second trimester	0.97	0.94, 1.01
Third trimester	0.94	0.85, 1.05
No prenatal care	2.51	2.22, 2.84
Tobacco Use	1.28	1.22, 1.35
High $PM_{2.5}$ exposure[2]		
Average over pregnancy	1.19	1.09, 1.30
First trimester	1.02	0.97, 1.07
Second trimester	0.96	0.90, 1.01
Third trimester	1.28	1.20, 1.37

1. Odds ratio estimates for covariates are adjusted for other factors listed in the first column of the table as well as parity, infant sex, year of birth, season of birth, and insurance type in the model with high average $PM_{2.5}$ exposure over pregnancy
2. The odds ratio estimates for first, second, third trimester high Pm2.5 exposure are from separate models with adjustment for the same covariates as listed above

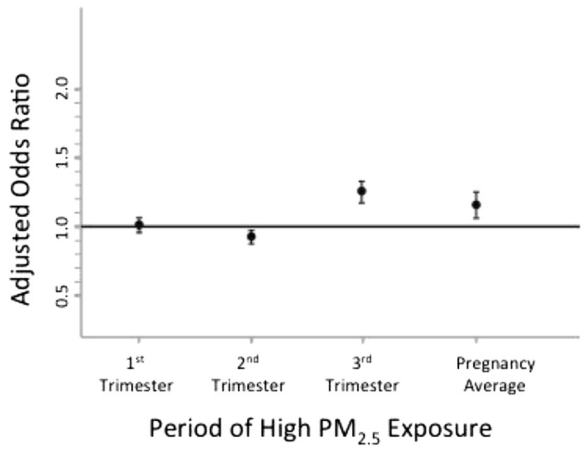


Fig. 3 Relative risk of preterm birth associated with exposure to high levels of $PM_{2.5}$, by trimester of pregnancy, Ohio 2007–2010

An association between air pollution and preterm birth was first suggested in an analysis of the Nashville Air Pollution Study that showed increased risk of death in preterm infants whose mothers were likely to be exposed with high levels of particulate pollution [15]. Subsequent studies have further explored the link between preterm birth and other air pollutants using measurements of a variety of pollutants (TSP, SO2, NOx, CO, and PM_{10}) in proximity to maternal residence, measured by stationary or remote sensing satellite monitors. These studies demonstrated mixed results with regard to associations with preterm birth and timing of high exposure periods during the pregnancy [16–21].

Prior studies that have attempted to link preterm birth specifically to $PM_{2.5}$ have also reported varied results. Gray et al. did not find significant effects in a study using EPA modeled data in North Carolina [6]. In a multi-country study, Fleisher found significant differences in preterm birth only in China when comparing areas with very high average $PM_{2.5}$ levels (>36.5 μg/m^3) compared to low levels (<12.5 μg/m^3) [22]. Recent studies using satellite measurements have also been mixed: Rudra [23] found no effect, Gehring [5] found a non-significant trend toward increased risk of preterm birth with increased $PM_{2.5}$ exposure, while Lee (2013) found high first trimester exposure was associated with modestly increased risk (OR 1.10 [1.01–1.20]) [24]. Jalaludin found that high $PM_{2.5}$ levels associated only with risk of preterm birth in pregnancies conceived in the winter (OR 1.426) [25]. Kloog found an increased risk of prematurity using a model that incorporated measured and estimated exposure values (OR 1.06 (1.01–1.13) per 10 μg/m^3 increase in third trimester) [9]. A recent meta-analysis combining previous studies found a modestly increased risk of preterm birth for each 10 μg/m^3 increase in $PM_{2.5}$ (OR 1.10 [1.03–1.18]); however, they

did not find evidence of increased risk in trimester specific exposures, as we identified in this study [26].

The $PM_{2.5}$ concentration threshold at which health is harmed is not well defined. We used the cutoff of 15 μg/m^3 average to define high exposure as this was the EPA National Ambient Air Quality standard for annual mean levels of $PM_{2.5}$ during the time period of the study. The standard was reduced to 12 μg/m^3 in 2012, after the EPA determined that the threshold level for harm may be in the 13–14 μg/m^3 range [27]. We used the cutoff of 15 μg/m^3 in these analyses because it may be more representative of exposure levels in relation to the EPA standard in our region during the time period of study. Using this threshold to define high exposure, we identified significant associations with preterm birth risk. However, when $PM_{2.5}$ exposure was modeled as a continuous variable, no risk increase for preterm birth was identified. This may suggest a threshold effect in which a critical level of exposure is necessary before harmful health effects are seen.

There are multiple mechanisms by which particulate matter may lead to deleterious health effects. Three broad pathways exist that may explain how air pollution may affect organs outside of the lung: 1) Toxic substances may enter the blood via the lungs and be carried throughout the circulation. 2) There may be a systemic oxidative stress and inflammatory response that is either triggered in the lungs, or by substances once they gain access to the general circulation. 3) Toxicants may disrupt the autonomic nervous system causing imbalance of sympathetic and parasympathetic systems. There is evidence of the importance for each of these pathways at the cellular and molecular level in non-pregnant humans, especially related to cardiovascular events [28]. It is plausible that any or all of these mechanisms may contribute to alterations in uteroplacental perfusion, nutrient and oxygen transfer to the fetus, or stimulate the inflammatory response that commonly precedes the onset of preterm parturition.

There are a number of methodological limitations of our study, which are common to studies examining exposure to ambient air pollution and birth outcomes: 1) Specific pollutants and their ambient concentrations not considered independently but rather grouped as $PM_{2.5}$. 2) Individual level exposure not quantified by personal sampling. Quantification of an individual's exposure is imprecise without either a completely controlled environment or portable sampling equipment – both of which are not practical for population cohort studies. 3) It is not known when the critical time for exposure is for specific outcomes. 4) Birth certificate data may not adequately describe potentially confounding socioeconomic or medical information. Regarding exposure quantification, there is likely some degree of sampling bias as EPA measurement stations are not randomly placed. Rather, monitoring sites are intended to capture ambient air levels and may be strategically placed to avoid major industrial sources of air, which could contribute to selection, and information bias. This misclassification could bias the results toward the null, and contribute to the lack of significant association identified when exposure was modeled in quartiles or as a continuous variable. Additionally, categorizing third trimester exposure as high levels occurring after 28 weeks would not account for early preterm births that occur prior to the third trimester. Despite statistical adjustment for available socioeconomic factors, unidentified socioeconomic factors or co-existent environmental risk factors may confound the interpretation of results in our study or similar studies. More populated areas tend to have higher proportions of patients with socioeconomic risk factors for preterm birth. Likely the best way to truly determine the connection between air pollution and preterm birth would be to have subjects carry continuous pollutant monitoring systems. This would allow more precise assessment of the threshold of risk and would allow us to further define behaviors associated with high pollutant exposure.

Conclusions

Our data suggest that women exposed to higher than the EPA standard exposure level of $PM_{2.5}$ over the course of pregnancy are at increased risk for preterm birth. Based on trimester-specific high exposure periods, high exposure during the third trimester of pregnancy are also significantly associated with increased preterm birth risk. While this study does not precisely define a safe threshold for exposure, it does support the EPA's decision to decrease the standard exposure limit of $PM_{2.5}$ concentration for individuals in the US. Additional research is needed to determine individual-level exposure as measured by ambient air and internal biomarkers of exposure and effect.

Abbreviations

adjOR: adjusted odds ratio; CO: carbon monoxide; EPA: Environmental Protection Agency; GEE: generalized estimating equations; NAAQS: US EPA National Ambient Air Quality Standard; NOx: nitrogen oxide; OR: odds ratio; PAR: Population attributable risk; PM_{10}: fine particulate matter, smaller than 2.5 μm; $PM_{2.5}$: Fine particulate matter smaller than 2.5 μm; PTB: Preterm birth; RR: relative risk; SO2: sulfer dioxide; TSP: trisodium phosphate.

Competing interests

The authors of this manuscript have no conflicts of interest or competing interests (financial or non-financial) to report.

Authors' contributions

Conceived and designed the study: ED MH EH AC ENH LM. Managed the data set including data preparation, performed data analyses and assisted with interpretation of the study findings: FX, EH, MH, AC. Analyzed the data: FX, EH, MH, AC. Contributed to writing and revising the manuscript: ED, WM, FX, EH, MH, ENH, LM, AC. All authors read and approved the final manuscript.

Acknowledgements
This work was supported by the Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, and March of Dimes Grant 22-FY13-543 for the March of Dimes Prematurity Research Center Ohio Collaborative. The funding sources for this study were not involved in the design or conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript. The decision to submit this manuscript for publication was made by the study authors without influence from the funding source.
This study includes data provided by the Ohio Department of Health which should not be considered an endorsement of this study or its conclusions.

Author details
[1]Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. [2]Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, 231 Albert Sabin Way, MSB Room 4553B, Cincinnati, OH 45267-0526, USA. [3]Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH, USA. [4]Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.

Received: 9 September 2015 Accepted: 10 January 2016
Published online: 15 January 2016

References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224–60.
2. Brook RD, Rajagopalan S. Particulate matter air pollution and atherosclerosis. Curr Atheroscler Rep. 2010;12(5):291–300.
3. Nieuwenhuijsen MJ, Dadvand P, Grellier J, Martinez D, Vrijheid M. Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. Environ Health. 2013;12:6.
4. Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect. 2008;116(5):680–6.
5. Gehring U, Wijga AH, Fischer P, de Jongste JC, Kerkhof M, Koppelman GH, et al. Traffic-related air pollution, preterm birth and term birth weight in the PIAMA birth cohort study. Environ Res. 2011;111(1):125–35.
6. Gray SC, Edwards SE, Schultz BD, Miranda ML. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. Environ Health. 2014;13(1):4.
7. Hannam K, McNamee R, Baker P, Sibley C, Agius R. Air pollution exposure and adverse pregnancy outcomes in a large UK birth cohort: use of a novel spatio-temporal modelling technique. Scand J Work Environ Health. 2014;40(5):518–30.
8. Huynh M, Woodruff TJ, Parker JD, Schoendorf KC. Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol. 2006;20(6):454–61.
9. Kloog I, Melly SJ, Ridgway WL, Coull BA, Schwartz J. Using new satellite based exposure methods to study the association between pregnancy PM2. 5 exposure, premature birth and birth weight in Massachusetts. Environ Health. 2012;11:40.
10. Pereira G, Bell ML, Lee HJ, Koutrakis P, Belanger K. Sources of fine particulate matter and risk of preterm birth in connecticut, 2000-2006: a longitudinal study. Environ Health Perspect. 2014;122(10):1117–22.
11. Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ Health Perspect. 2009;117(11):1773–9.
12. Padula AM, Mortimer KM, Tager IB, Hammond SK, Lurmann FW, Yang W, et al. Traffic-related air pollution and risk of preterm birth in the San Joaquin Valley of California. Ann Epidemiol. 2014;24(12):888–95e4.
13. Ha S, Hu H, Roussos-Ross D, Haidong K, Roth J, Xu X. The effects of air pollution on adverse birth outcomes. Environ Res. 2014;134:198–204.
14. US Environmental Protection Agency. AirData. Available from: http://www.epa.gov/airdata/. Accessed 28 May 2015.
15. Sprague HA, Hagstrom R. The Nashville Air Pollution Study: mortality multiple regression. Arch Environ Health. 1969;18(4):503–7.
16. Xu X, Ding H, Wang X. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. Arch Environ Health. 1995;50(6):407–15.
17. Landgren O. Environmental pollution and delivery outcome in southern Sweden: a study with central registries. Acta Paediatr. 1996;85(11):1361–4.
18. Bobak M. Outdoor air pollution, low birth weight, and prematurity. Environ Health Perspect. 2000;108(2):173–6.
19. Ritz B, Yu F, Chapa G, Fruin S. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. Epidemiology. 2000;11(5):502–11.
20. Lin MC, Chiu HF, Yu HS, Tsai SS, Cheng BH, Wu TN, et al. Increased risk of preterm delivery in areas with air pollution from a petroleum refinery plant in Taiwan. J Toxic Environ Health A. 2001;64(8):637–44.
21. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect. 2003;111(14):1773–8.
22. Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, Betran AP, et al. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health. Environ Health Perspect. 2014;122(4):425–30.
23. Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA. Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in western Washington State. Environ Health Perspect. 2011;119(6):886–92.
24. Lee PC, Roberts JM, Catov JM, Talbott EO, Ritz B. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J. 2013;17(3):545–55.
25. Jalaludin B, Mannes T, Morgan G, Lincoln D, Sheppeard V, Corbett S. Impact of ambient air pollution on gestational age is modified by season in Sydney, Australia. Environ Health. 2007;6:16.
26. Zhu X, Liu Y, Chen Y, Yao C, Che Z, Cao J. Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis. Environ Sci Pollut Res Int. 2015;22(5):3383–96.
27. National Ambient Air Quality Standards for Particulate Matter; Final Rule, Fed. Reg. Vol. 78, No. 10 (January 15, 2013) (to be codified at 40 CFR Parts 50, 51, 52, 53, and 58). Print. www.gpo.gov/fdsys/pkg/FR-2013-01-15/pdf/2012-30946.pdf. Accessed 28 May 2015.
28. Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, et al. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. Hypertension. 2009;54(3):659–67.

NEW SOLUTIONS, Vol. 23(1) 55-83, 2013

Scientific Solutions

INVESTIGATING LINKS BETWEEN SHALE GAS DEVELOPMENT AND HEALTH IMPACTS THROUGH A COMMUNITY SURVEY PROJECT IN PENNSYLVANIA

NADIA STEINZOR
WILMA SUBRA
LISA SUMI

ABSTRACT

Across the United States, the race for new energy sources is picking up speed and reaching more places, with natural gas in the lead. While the toxic and polluting qualities of substances used and produced in shale gas development and the general health effects of exposure are well established, scientific evidence of causal links has been limited, creating an urgent need to understand health impacts. Self-reported survey research documenting the symptoms experienced by people living in proximity to gas facilities, coupled with environmental testing, can elucidate plausible links that warrant both response and further investigation. This method, recently applied to the gas development areas of Pennsylvania, indicates the need for a range of policy and research efforts to safeguard public health.

Keywords: health surveys, shale gas, toxic exposure, hydraulic fracturing, fracking

> Public health was not brought into discussions about shale gas extraction at earlier stages; in consequence, the health system finds itself lacking critical information about environmental and public health impacts of the technologies and unable to address concerns by regulators at the federal and state levels, communities, and workers. . . .
>
> —Institute of Medicine at the National Academies of Science [1]

doi: http://dx.doi.org/10.2190/NS.23.1.e
http://baywood.com

For many years, extracting natural gas from deep shale formations across the United States (such as the Marcellus Shale in the East or the Barnett Shale in Texas) was considered economically and technologically infeasible. More recently, changes in hydraulic fracturing technology and its combination with horizontal drilling have made it possible to drill much deeper and farther. Bolstered by declining global oil resources and a strong political push to expand domestic energy production, this has resulted in a boom in shale gas production nationwide and projections of tens or even hundreds of thousands of wells being drilled in the coming decades.

By mid-2012, there were nearly 490,000 producing natural gas wells in the United States, 60,000 more than in 2005 [2]. In Pennsylvania alone, more than 5,900 unconventional oil and gas wells had been drilled, and more than 11,700 had been permitted, between 2005 and September 2012; the pace of expansion has been rapid, with 75 percent of all unconventional wells drilled just in the last two years [3]. The rapid pace of industry expansion is increasingly divergent from the slower pace of scientific understanding of its impacts, as well as policy and regulatory measures to prevent them—in turn raising many questions that have yet to be answered [4]. Further, the limited availability of information has both contributed to the public perception and supported industry assertions that health impacts related to oil and gas development are isolated and rare.

Modern-day industrial gas and oil development has many stages, uses a complex of chemicals, and produces large volumes of both wastewater and solid waste, which create the potential for numerous pathways of exposure to substances harmful to health, in particular to air and water pollution [5]. Many reports of negative health impacts by people living in proximity to wells and oil and gas facilities have been documented in the media and through research by organizations [6-8]. In addition, several self-reporting health survey and environmental testing projects have been conducted in response to complaints following pollution events or the establishment of facilities [9-12].

Such short-term projects have been initiated in a research context in which longer-term investigations—particularly ones that seek to establish causal links between health problems and oil and gas development—have historically been narrow and inconsistent [13]. Reflecting growing concern over the need to deepen knowledge among scientists, public agency representatives, and environmental and health professionals, four conferences on the links between shale gas development and human health were convened in just a one-year period (November 2011–November 2012), including by the Graduate School of Public Health at the University of Pittsburgh; by Physicians, Scientists, and Engineers for Healthy Energy; and by the Institute of Medicine of the National Academy of Sciences.

In-depth research on the health impacts of oil and gas development has also begun to appear in the literature. In 2011, a review of more than 600 known chemicals used in natural gas operations concluded that many could cause cancer

and mutations and have long-term health impacts (including on the skin, eyes, and kidneys and on the respiratory, gastrointestinal, brain/nervous, immune, endocrine, and cardiovascular systems) [14]. In early 2012, a study by researchers at the University of Colorado concluded that the toxicity of air emissions near natural gas sites puts residents living close by at greater risk of health-related impacts than those living farther away [15]. Also in 2012, a paper (published in this journal) documented numerous cases in which livestock and pets exposed to toxic substances from natural gas operations suffered negative health impacts and even death [16].

Public health has not been a priority for decision-makers confronting the expansion of natural gas development and consumption. Commissions to study the impacts of shale gas development have been established by Maryland and Pennsylvania and by the U.S. Secretary of Energy, but of the more than 50 members on these official bodies, none had health expertise [17]. In addition, state and federal agencies in charge of reviewing energy proposals and issuing permits do not require companies to provide information on potential health impacts, while only a few comprehensive health impact assessments (HIAs) on oil and gas development have ever been conducted in the United States [18]. Data on air and water quality near oil and gas facilities are also lacking because federal environmental testing and monitoring has long focused on a limited number of air contaminants and areas of high population density [19], while testing at oil and gas facilities in states like Pennsylvania began only recently [20]. Finally, only a few states (including Pennsylvania, Ohio, and Colorado) have any requirements for baseline air and water quality testing before drilling begins, making it difficult for researchers and regulators—as well as individuals who are directly impacted—to establish a clear connection afterwards.

SUMMARY OF THE RELEVANCE OF SELF-REPORTING HEALTH SURVEYS

For many individuals and communities living amidst oil and gas development and experiencing rapid change in their environments, too much can be at stake to rely solely on the results of long-term studies, especially those that are just now being developed. Recent examples include a new study by Guthrie Health and the Geisinger Health System in Pennsylvania, set to take from 5 to 15 years [21], and research proposals solicited in April 2012 by the National Institute of Environmental Health Sciences [22].

In contrast, self-reporting health survey research facilitates the collection and analysis of data on current exposures and medical symptoms—thereby helping to bridge the prevailing knowledge gap and pointing the way toward possible policy changes needed to protect public health. Another premise throughout the various phases of this project (location selection, survey distribution and completion, environmental testing, report development and distribution, and

outreach to decision-makers) was the value of public participation in science and the engagement of a variety of actors and networks to both conduct the research and ensure its beneficial application [23].

With this in mind, this health and testing project reflects some of the core principles of community-based participatory research (CBPR), including an emphasis on community engagement, use of strengths and resources within communities, application of findings to help bring about change, and belief in the research relevance and validity of community knowledge [24]. For example, the current project selected areas for investigation based in part on the observations of change in environmental conditions by long-time residents, and upon completion, participants received resources on air and water testing and reporting of drilling problems for use in their communities.

In addition, CBPR is often used by public agencies and academic researchers to gather information on health conditions that may be related to social or environmental factors manifested on the community as well as individual level [25]. Relevant examples include identification of linkages between environmental health and socioeconomic status [26], adverse health impacts associated with coal mining [27], and the perception of health problems from industrial wind turbines [28].

Community survey and environmental testing projects such as the current one are also valuable in identifying linkages and considerations that can be used to develop protocols for additional research and policy measures. For example, community survey projects similar to the current one have revealed the presence of toxic chemicals in water and air that were known to be associated with health symptoms reported by residents, resulting in the strengthening of state standards for the control of drilling-related odors in Texas [9], expansion of a groundwater contamination investigation by the U.S. Environmental Protection Agency in Wyoming [10], and relocation of residential communities away from nearby oil refineries and contaminated waste storage areas in Louisiana [29].

METHODS

Between August 2011 and July 2012, a self-reporting health survey and environmental testing project was undertaken in order to:

- investigate the extent and types of health symptoms experienced by people living in the “gas patches” (that is, gas development areas) of Pennsylvania;
- provide air and water quality testing to some of the participating households in need of such information;
- identify possible connections between health symptoms and proximity to gas extraction and production facilities;
- provide information to researchers, officials, regulators, and residents concerned about the impact of gas development on health and air and water quality; and

- make recommendations for both further research and the development of policy measures to prevent negative health and environmental impacts.

This project did not involve certain research elements, such as structured control groups in non-impacted areas and in-depth comparative health history research, that aim to show a direct cause-and-effect relationship or to rule out additional exposures and risks. Such work, while important, was beyond the scope of the project.

The primary routes of exposure to chemicals and other harmful substances used and generated by oil and gas facilities are inhalation, ingestion, and dermal absorption—of substances in air, drinking water, or surface water—which can lead to a range of symptoms. The health survey instrument explored such variations in exposure through checklists of health symptoms grouped into categories (skin, sinus/respiratory, digestive/stomach, vision/eyes, ear/nose/mouth, neurological, urinary/urological, muscles/joints, cardiac/circulatory, reproductive, behavioral/mood/energy, lymphatic/thyroid, and immunological). A similar structure was followed for different categories of problems in participants' disease history (kidney/urological, liver, bones/joints, ulcers, thyroid/lymphatic, heart/lungs, blood disorders, brain/neurological, skin/eyes/mouth, diabetes, and cancer). Questions were also asked about occupational background and related toxic exposure history. In addition, the survey included questions on proximity to three types of facilities (compressor and pipeline stations, gas-producing wells, and impoundment or waste pits) to explore possible sources of exposure. It also asked participants to describe the type and frequency of odors they observe, since odors can both indicate the presence of a pollutant and serve as warning signs of associated health risks [30].

As indicated in Table 1, the survey was completed by 108 individuals (in 55 households) in 14 counties across Pennsylvania, with the majority (85 percent) collected in Washington, Fayette, Bedford, Bradford, and Butler counties. Taken together, the counties represent a geographical range across the state and have active wells and other facilities that have increased in number in the past few years, allowing reports of health impacts and air and water quality concerns by residents to surface [31, 32]. The survey and testing locations were all in rural and suburban residential communities.

All survey participants were assured that their names, addresses, and other identifying information on both the surveys and environmental testing results would be kept confidential and used only for purposes related to this project, such as following up with clarifying questions, responding to requests for assistance, or providing resources. Due to expressed concerns about confidentiality, participants had the option of completing the surveys anonymously, which some chose to do. Most participants answered questions on their own. In some cases, spouses, parents, or neighbors completed surveys for participants, and a few provided answers to the project coordinator in person or over the phone.

Table 1. Survey Locations

County surveyed	Number of surveys collected and percent of all surveys
Washington	24 (22%)
Fayette	20 (18%)
Bedford	20 (18%)
Bradford	17 (16%)
Butler	12 (11%)
Jefferson	3 (3%)
Sullivan	2 (2%)
Greene	2 (2%)
Warren	2 (2%)
Elk	2 (2%)
Clearfield	1 (1%)
Erie	1 (1%)
Susquehanna	1 (1%)
Westmoreland	1 (1%)
Total	108

While less formal and structured, the approach taken to identifying project participants has similarities to established non-random research methods that are respondent-driven and rely on word-of-mouth and a chain of referrals to reach more participants, such as "snowball" and "network" sampling [33]. As in studies in which these methods are used, the current project had a specific purpose in mind, focused on a group of people that can be hard to identify or reach, and had limited resources available for recruitment [34].

The survey was distributed in print form either by hand or through the mail and was initiated through existing contacts in the target counties. These individuals then chose to participate in the project themselves and/or recommended prospective participants, who in turn provided additional contacts. The survey was also distributed to individuals who expressed interest in participating directly to the project coordinator at public events or through neighbors, family members, and friends who had already completed surveys.

A second phase of the project involved environmental testing conducted at the homes (i.e., in the yards, on porches, or at other locations close to houses) of a

subset of the survey participants (70 in total) in order to identify the presence of pollutants that may be coming from gas development facilities. In all, 34 air tests and nine water tests were conducted at 35 households. Test locations were selected based on household interest, the severity of symptoms reported, and proximity to gas facilities; results were made available to the households where the testing took place. The air tests were conducted with Summa Canisters put out for 24 hours by trained individuals and the results analyzed with TO-14 and TO-15 methods, which are used and approved by the U.S. Environmental Protection Agency to test for volatile organic compounds (VOCs) such as benzene, toluene, ethylbenzene, and xylene (known as BTEX chemicals). The water tests were based on samples drawn directly from household sinks or water wells by technicians employed by certified laboratories and covered the standard Tier 1, Tier 2, and Tier 3 (including VOCs/BTEX) and in one case, gross alpha/beta radiation, radon, and radium.

FINDINGS

Health Surveys

Among participants, 45 percent were male, ranging from 18 months to 79 years of age, and 55 percent were female, ranging from 7 to 77 years of age. The closest a participant lived to gas facilities was 350 feet and the farthest away was 5 miles.

Participants had a wide range of occupational backgrounds, including animal breeding and training, beautician, child care, construction, domestic work, farming, management, mechanic, medical professional, office work, painter, retail, teaching, and welding. About 20 percent of participants reported an occupation-related chemical exposure (for example, to cleaning products, fertilizers, pesticides, or solvents). At the time of survey completion, 80 percent of participants did not smoke and 20 percent did. More than 60 percent of the current nonsmokers had never smoked, although 20 percent of nonsmokers lived with smokers.

Almost half of the survey participants answered the question on whether they had any health problems prior to shale gas development. A little less than half of those responses indicated no health conditions before the development began and a little more than half reported having had one or just a few—in particular allergies, asthma, arthritis, cancer, high blood pressure, and heart, kidney, pulmonary, and thyroid conditions were named by respondents.

While not asked specifically in the survey, some participants volunteered (verbally or in writing) additional information that points to health-related concerns warranting further investigation. For example, five reported that their existing health symptoms became worse after shale gas development started and 15 that their symptoms lessened or disappeared when they were away from home. Participants in 22 households reported that pets and/or livestock had unexplained symptoms (such as seizures or losing hair) or suddenly fell ill and died after gas development began nearby.

Some variation was noted with regard to the specific symptoms reported for each category surveyed, and some symptoms were reported to a notable degree in only one or a few locations. However, as seen in Table 2, the same overall categories of problems reported by survey participants garnered high response rates among survey participants regardless of region or county. For example, sinus/respiratory problems garnered the highest percentage of responses by participants overall, as well as in four of the five focus counties; the second top complaint category, behavioral/mood/energy, was the first in one county, second in three, and fourth in one. The total number of symptoms reported by individual participants ranged from 2 to 111; more than half reported having more than 20 symptoms and nearly one-quarter reported more than 50 symptoms. The highest numbers were reported by a 26-year-old female in Fayette County (90), a 51-year-old female in Bradford County (94), and a 59-year-old female in Warren County (111).

The 25 most prevalent individual symptoms among all participants were increased fatigue (62%), nasal irritation (61%), throat irritation (60%), sinus problems (58%), eyes burning (53%), shortness of breath (52%), joint pain (52%), feeling weak and tired (52%), severe headaches (51%), sleep disturbance (51%), lumbar pain (49%), forgetfulness (48%), muscle aches and pains (44%), difficulty breathing (41%), sleep disorders (41%), frequent irritation (39%), weakness (39%), frequent nausea (39%), skin irritation (38%), skin rashes (37%), depression (37%), memory problems (36%), severe anxiety (35%), tension (35%), and dizziness (34%).

Many symptoms were commonly reported regardless of the distance from the facility (in particular sinus problems, nasal irritation, increased fatigue, feeling weak and tired, joint pain, and shortness of breath). In addition, there was some variability in the percentage of respondents experiencing certain symptoms in relation to distance from facility, including higher rates at longer distances in a few instances. Possible influencing factors could include topography, weather conditions, participant reporting, the use of emission control technologies at facilities, or type of production (e.g., wet gas contains higher levels of liquid hydrocarbons than dry gas).

However, many symptoms showed a clearly identifiable pattern: as the distance from facilities increases, the percentage of respondents reporting the symptoms generally decreases [35]. For example, when a gas well, compressor station, and/or impoundment pit were 1500-4000 feet away, 27 percent of participants reported throat irritation; this increased to 63 percent at 501-1500 feet and to 74 percent at less than 500 feet. At the farther distance, 37 percent reported sinus problems; this increased to 53 percent at the middle distance and 70 percent at the shortest distance. Severe headaches were reported by 30 percent of respondents at the farther distance, but by about 60 percent at the middle and short distances.

Table 2. Percent of Participants Reporting Symptoms in the Most Prevalent Categories of Symptoms, by County

		Percent of individuals reporting symptoms in category					
Symptom category	All counties	Bedford	Bradford	Butler	Fayette	Washington	Others[a]
Sinus/respiratory	88	80	82	75	85	95	87
Behavioral/mood/energy	80	60	88	67	85	74	67
Neurological	74	45	71	50	70	79	60
Muscles/joints	70	55	82	67	70	74	47
Digestive/stomach	64	55	65	58	75	63	33
Ear/nose/mouth	66	40	59	50	75	68	47
Skin reactions	64	45	70	67	75	63	27
Vision/eyes	63	40	65	50	70	79	53

[a]Includes Clearfield, Elk, Erie, Jefferson, Greene, Sullivan, Susquehanna, Warren, and Westmoreland counties. The surveys from these counties (15) were analyzed together to create a group comparable in number to each of the counties where more surveys were collected.

Figure 1 shows, for the top 20 symptoms, the percentage of residents living within 1500 feet of a natural gas facility (well, compressor, or impoundment) who reported the symptom, compared to the percentage among residents living more than 1500 feet from the facility. For 18 of the 20 symptoms, a higher percentage of those living within 1500 feet of a facility experienced the symptom than of those living further away.

The difference in percentages reporting the symptom in the two groups (i.e., 1500 feet or closer vs. more than 1500 feet from a facility) was statistically significant for 10 of the 20 symptoms. Notably, this finding reinforces the value of data attained through self-reporting health surveys. It shows that, regardless of how symptom data were acquired, they suggest that increased proximity to gas facilities has a strong association with higher rates of symptoms reported.

When the most prevalent symptoms are broken out by age and distance from facility, some patterns stand out [35]. Within each age group, the subset living within 1500 feet of any oil and gas facility had a higher percentage of most symptoms than the age group as a whole.

Among the youngest respondents (1.5-16 years of age), for example, those within 1500 feet experienced higher rates of throat irritation (57% vs. 69%) and severe headaches (52% vs. 69%). It is also notable that the youngest group had the highest occurrence of frequent nosebleeds (perhaps reflective of the more sensitive mucosal membranes in the young), as well as experiencing conditions not typically associated with children, such as severe headaches, joint and lumbar pain, and forgetfulness.

Among 20- to 40-year-olds, those living within 1500 feet of a facility reported higher rates of nearly all symptoms; for example, 44 percent complained of frequent nosebleeds, compared to 29 percent of the entire age group. The same pattern existed among 41- to 55-year-olds with regard to several symptoms (e.g., throat and nasal irritation and increased fatigue), although with smaller differences and greater variability than in the other age groups.

The subset of participants in the oldest group (56- to 79-year-olds) living within 1500 feet of facilities had much higher rates of several symptoms, including throat irritation (67% vs. 47 %), sinus problems (72% vs. 56%), eye burning (83% vs. 56%), shortness of breath (78% vs. 64%), and skin rashes (50% vs. 33%).

In sum, while these data do not prove that living closer to oil and gas facilities causes health problems, they do suggest a strong association since symptoms are more prevalent in those living closer to facilities than those living further away. Symptoms such as headaches, nausea, and pounding of the heart are known to be the first indications of excessive exposure to air pollutants such as VOCs [36], while the higher level of nosebleeds in the youngest age group is also consistent with patterns identified in health survey projects in other states [9, 10].

The survey also asked respondents to indicate whether they were smokers. While the average number of symptoms for smokers was higher for smokers than nonsmokers (30 vs. 22), the most frequently reported symptoms were very

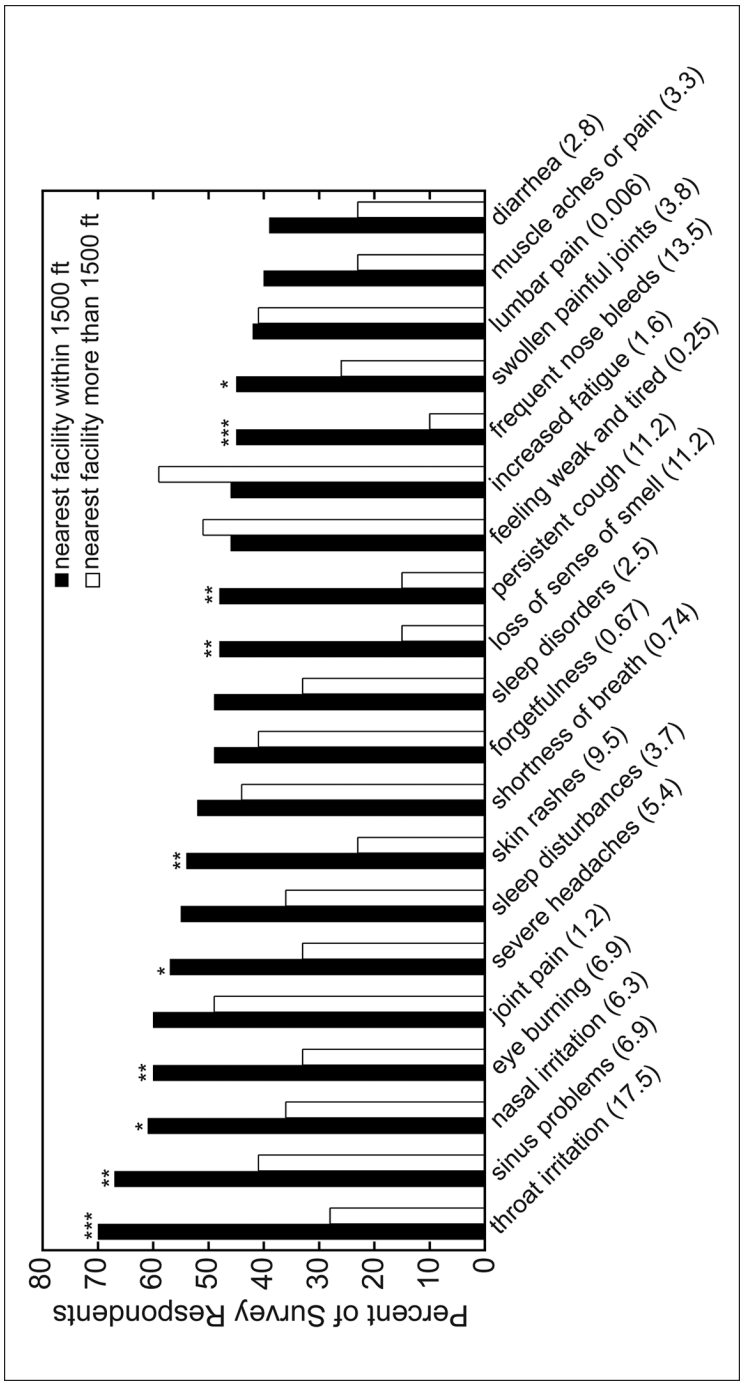


Figure 1. Association of symptoms and distance from facilities.

Note: The significance of the effect was tested using a two-way contingency table analysis, and the chi-square value is given in parenthesis after each symptom. Effects significant at $p < 0.001$ are indicated by ***, those significant at $p < 0.01$ by **, and those significant at $p < 0.05$ by *.

similar (including forgetfulness, increased fatigue, lumbar pain, joint pain, eye burning, nasal irritation, sinus problems, sleep disturbances, severe headaches, throat irritation, shortness of breath, frequent nausea, muscle aches or pains, and weakness). The fact that the nonsmokers experienced symptoms that are commonly considered to be side effects of smoking (e.g., persistent hoarseness, throat irritation, sinus problems, nasal irritation, shortness of breath, and sleep disturbances) suggests that factors other than smoking were at play.

In addition, while the smoking subpopulation generally reported a larger number of symptoms, the symptoms most frequently reported by smokers and nonsmokers were remarkably similar within each age group [35]. For example, for 20- to 40-year-olds, increased fatigue, sinus problems, throat irritation, frequent nausea, and sleep problems were among the top symptoms for both smokers and nonsmokers. In the 41- to 55-year-old group, increased fatigue, throat irritation, eye burning, severe headaches, and nasal irritation were among the top symptoms for both smokers and nonsmokers, and in the over-55 age group, eye burning, sinus problems, increased fatigue, joint pain, and forgetfulness were among the top symptoms of both smokers and nonsmokers.

Participants were asked if they had noticed any odors and were asked whether they knew the source of the odors. In all but a few cases, survey participants mentioned only gas-related sources. Responses focused on locations, facilities, and processes, including drilling, gas wells, well pads, fracturing, compressor stations, condensate tanks, flaring, impoundments and pits, retention ponds, diesel engines, truck traffic, pipelines and pipeline stations, spills and leaks, subsurface ground events or migrations from underground, seismic testing, blue-colored particles in the air (possibly catalytic compounds or particulate matter), and water and stock wells. Odors were among the most common of complaints, with 81 percent of participants experiencing them sometimes or constantly. The frequency ranged from one to seven days per week and from several times per day to all day long; 18 percent said they could smell odors every day.

Participants were also asked to describe odors and whether they noticed any health symptoms when odor events occurred. The most prevalent links between odors and symptoms reported were:

- *nausea:* ammonia, chlorine, gas, propane, ozone, rotten gas;
- *dizziness:* chemical burning, chlorine, diesel, ozone, petrochemical smell, rotten/sour gas, sulfur;
- *headache:* chemical smell, chlorine, diesel, gasoline, ozone, petrochemical smell, propane, rotten/sour gas, sweet smell;
- *eye/vision problems:* chemical burning, chlorine, exhaust;
- *respiratory problems*: ammonia, chemical burning, chlorine, diesel, perfume smell, rotten gas, sulfur;
- *nose/throat problems:* chemical smell, chlorine, exhaust, gas, ozone, petrochemical smell, rotten gas, sulfur, sweet smell;

- *nosebleeds:* kerosene, petrochemical smell, propane, sour gas;
- *skin irritation:* chemical smell, chlorine, ozone, sulfur;
- *decreased energy/alertness:* chemical gas, ozone, rotten/sour gas, sweet smell; and
- *metallic/bad taste in mouth:* chemical burning, chlorine, turpentine.

Environmental Testing

As detailed in Table 3, the air tests detected a total of 19 VOCs in ambient air sampled outside of homes.

The number of compounds detected in a single sample ranged from one to 25; there was some consistency with regard to the chemicals present in most of the samples, although the concentrations of VOCs detected varied across counties [35]. The highest numbers of VOCs were detected in air samples from Washington County (15), Butler County (15), Bradford County (12), and Fayette County (9). Washington County also had the highest measured concentration of five VOCs and the second highest concentration of 12 chemicals. Samples from Butler and Bradford Counties had the highest concentrations of five and three VOCs, respectively. Five chemicals were detected in all nine of the samples from Washington County and in the six samples from Butler County: 1,1,2-trichloro-1,2,2-trifluoroethane, carbon tetrachloride, chloromethane, toluene, and trichlorofluoromethane.

It is also possible that in some places, sampling did not occur at the precise times when facilities were emitting high concentrations of chemicals or when the wind was blowing contaminants toward canisters. Some of the additional variation in number of chemicals and concentrations could be due to differences in topography, the total number of active oil and gas wells, the types of wells (conventional versus unconventional), the use of emission control technologies, and the number of active drilling sites, compressor stations, and oil and gas waste impoundments located within a certain radius of the sampling locations.

In 2010, the Pennsylvania Department of Environmental Protection (DEP) conducted air testing around natural gas wells and facilities in three regions across the state, in part using the same canister sampling methods as in this project [37]. When compared to DEP's results, our results showed some striking similarities in both the chemicals detected and concentrations. In particular, BTEX chemicals that we measured in Butler and Washington counties were consistently higher than concentrations found at DEP control sites (ethylbenzene and — and *p*-xylenes were not detected at any of the control sites). When compared to the sampling done by DEP around oil and gas facilities, the concentrations in Butler and Washington counties were in the same range for benzene, but were considerably higher for toluene, ethylbenzene and *m*- and *p*-xylenes. It is also striking that some of the concentrations of ethylbenzene and

Table 3. Volatile Organic Compounds (VOCs) in Ambient Air, Sorted by Percent Detection[a]

Compound	Total number of samples	Number of samples detecting VOCs	Percent of samples detecting VOCs	Minimum concentration	Maximum concentration	Chemical reporting limits for the three labs		
						Columbia	Con-Test	Pace[b]
2-Butanone	17	16	94	0.95	2.9	0.85-1.3	NA	NA
Acetone	17	15	88	8.0	19	6.5-10	NA	NA
Chloromethane	34	27	79	1.0	1.66	0.59-0.90	0.1	1.39-1.53
1,1,2-Trichloro-1,2,2-trifluoroethane	34	26	76	0.54	0.73	0.22-0.34	0.38	5.13-5.67
Carbon tetrachloride	34	26	76	0.4	0.76	0.091-0.14	0.31	4.21-4.65
Trichlorofluoromethane	34	26	76	0.6	1.8	0.81-1.2	0.28	3.32-3.66
Toluene	34	22	65	0.68	7.9	0.53-0.82	0.19	2.52-2.79
Dichlorodifluoromethane	17	9	63	1.9	2.8	NA	0.25	3.32-3.66
n-Hexane	8	3	38	3.03	7.04	NA	NA	2.37-2.61
Benzene	34	11	32	0.31	1.5	0.46-0.67	0.16	2.14-2.36

Methylene chloride	34	10	29	1.9	32.62	0.49-0.76	1.7	2.33-2.57
Total hydrocarbons (gas)[c]	8	2	25	49.8	146	NA	NA	46.9-52.2
Tetrachloroethylene	34	8	24	0.12	10.85	0.10-0.16	0.34	4.54-5.02
1,2,4-Trimethylbenzene	17	4	24	0.38	0.61	NA	0.25	3.30-3.64
Ethylbenzene	34	6	1	0.27	1.5	1.4-1.9	0.22	2.91-3.21
Trichloroethylene	34	6	18	0.17	5.37	0.08-0.12	0.27	3.60-3.98
Xylene (— and *p*-)	34	5	15	0.92	5.2	2.5-3.8	0.43	2.82-3.12
Xylene (*o*)	34	5	15	0.39	1.9	1.2-1.9	0.22	2.91-3.21
1,2-Dichloroethane	34	1	3	0.64	0.64	0.59-0.90	0.2	2.71-2.99

[a]Concentrations are in micrograms per cubic meter, $\mu g/m^3$ (n = total number of canister samples that were analyzed for a particular chemical).

[b]Pace Lab's reporting limits were in parts per billion volume (ppbv). We converted to micrograms per cubic meters ($\mu g/m^3$) using equations in the Air Unit Conversion Table (Torrent Labs, www.torrentlab.com/torrent/Home/ResourceCenter.html).

[c]Total hydrocarbons reported as parts per billion volume (ppbv).

xylene measured at rural and suburban residential homes in Butler and Washington counties were higher than any concentration detected by the DEP at the Marcus Hook industrial site in 2010.

As stated above, several factors can influence air results. However, it is also highly possible that the poorer air quality in the areas where we tested—which were rural and residential, with little or no other industry nearby—can be attributed to gas facilities. While the DEP reports on the agency's air testing indicated that some of the VOCs we found in our study may not be due to oil and gas development since they persist in the atmosphere and have been widely used (for example, as refrigerants), the agency also indicates that acetone and the BTEX chemicals can be attributed to gas development [37].

With regard to the water tests conducted, Table 4 shows the 26 parameters that were detected in at least one sample. More than half of the project water samples contained methane; although some groundwater contains low concentrations of methane under normal conditions, this finding could also indicate natural gas migration from casing failure or other structural integrity problems [38]. Four of the substances detected in water well samples in Bradford and Butler Counties—manganese, iron, arsenic, and lead—were found at levels that exceed the Maximum Contaminant Levels (MCLs) set by Pennsylvania DEP's Division of Drinking Water Management [39]. Two of the water samples, both from Butler County, were more acidic than the recommended pH for drinking water.

Some metals, such as manganese and iron, are elevated in Pennsylvania surface waters and soils, either naturally or due to past industrial activities, and levels can vary regionally [40]. In 2012, Pennsylvania State University (PSU) researchers found that some drinking water wells in the state contained somewhat elevated concentrations of certain contaminants prior to any drilling in the area [41]. However, seven out of the nine water supplies sampled in our study (78%) had manganese levels above the state MCL—a much higher percentage than what was found in the pre-drilling samples in the PSU study (27%). Even where metals are naturally occurring or predate gas development, drilling and hydraulic fracturing can contribute to elevated concentrations of these contaminants [42] and have the potential to mobilize substances in formations such as Marcellus Shale, which is enriched with barium, uranium, chromium, zinc, and other metals [43].

LINKAGES BETWEEN SURVEYS AND ENVIRONMENTAL TESTING

More research would be required to identify cause-and-effect connections between the chemicals present in air and water in Pennsylvania's gas patches and symptoms reported by residents in specific locations. Nonetheless, such links are plausible since many of the chemicals detected in the testing are

known to be related both to oil and gas operations and to the health symptoms reported by individuals living at the sites where air and water testing was conducted [13-15].

The air tests together detected 19 chemicals that are known to cause sinus, skin, ear/nose/mouth, and neurological symptoms, 17 that may affect vision/eyes, and 16 that may induce behavioral effects; as well as 11 that have been associated with liver damage, nine with kidney damage, and eight with digestive/stomach problems. In addition, the brain and nervous system may be affected by five of the VOCs detected, the cardiac system by five, muscle by two, and blood cells by two [44, 45].

Using these sources [44, 45], we compared lists of the established health effects of the chemicals detected at households where testing occurred with lists of the symptoms reported in surveys by participants at those testing locations in order to identify associations. We then calculated the rate of association, in which the denominator is the total number of health impacts reported by an individual and the numerator is the total number of health impacts reported by that individual that are consistent with the known health impacts of the chemicals detected through air or water testing where they live.

Benzene, toluene, ethylbenzene, xylene, chloromethane, carbon disulfide, trichloroethylene (TCE), and acetone were detected through testing at the same households where survey participants reported symptoms established in the literature [13-15, 44, 45] as associated with these chemicals, including symptoms in the categories of sinus/respiratory, skin, vision/eyes, ear/nose/mouth, and neurological. Some of these chemicals, as well as others (such as carbon tetrachloride and tetrachloroethylene) were found at sites where survey participants reported known associated symptoms in the categories of digestion, kidney and liver damage, and muscle problems. Specific examples of chemicals and symptoms that are linked in the research literature, and were found together at households where testing and surveys were conducted, are: benzene and dizziness and nasal, eye, and throat irritation; carbon tetrachloride and nausea, headaches, and liver and kidney disease; and tetrachloroethylene and skin rashes, persistent cough, and nerve damage.

As shown in Table 5, health symptoms reported by the individuals living in a home where testing occurred matched the known health effects of chemicals detected in that home at an overall rate of 68 percent. Fayette and Washington counties had the highest match, followed by Greene, Bedford, and Butler counties.

In addition, the percent of individuals reporting symptoms that have been associated with chemicals detected in air testing at households participating in this study showed some consistency across counties with regard to the most significant categories of problems reported, as shown in Table 6—indicating that patterns in both chemicals detected and symptoms exist despite different geographic locations.

Table 4. Water Quality Results from Nine Private Water Wells in Bradford and Butler Counties, Pennsylvania

Parameter[a]	Units	Number of samples	Number above detection limit	Minimum[b]	Maximum	Mean[c]	PA DEP MCL[d]	Number of samples above MCL[e]
Barium	mg/L	9	9	0.029	0.5	0.25	2	0
Calcium	mg/L	9	9	33	66.2	43.7	None	
Magnesium	mg/L	9	9	4.5	16.8	9.1	None	
Sodium	mg/L	9	9	9.2	64.1	20.9	None	
Strontium	mg/L	9	9	0.126	1.7	0.5	None	
Hardness (total as $CaCO_3$)	mg/L	9	9	120	234	147	None	
pH	Std Units	9	9	6	7.9	6.5	6.5-8.5	[f]
Alkalinity (total as $CaCO_3$)	mg/L	9	9	38	285	130	None	
Total dissolved solids	mg/L	9	9	138	392	218	500	0
Sulfate	mg/L	9	9	6.7	231	33	250	0
Manganese	mg/L	9	7	< 0.005	6.44	1.04	0.05	7
Chloride	mg/L	9	7	< 5.0	84.3	24.1	250	0
Iron	mg/L	9	6	< 0.04	153	19.5	0.3	5
Potassium	mg/L	6	6	1.14	1.57	1.1	None	

Specific conductance	μmhos/cm	6	6	287	552	326	None	
Methane	μg/L	9	5	1.06	57.4	10	0.3	
Arsenic	mg/L	9	4	< 0.001	0.0282	0.005	0.010	1
Lead	mg/L	9	4	< 0.001	0.113	0.113	0.01	3
Total coliform	per 100 mL	9	4	Absent	Present		None	
Total suspended solids	mg/L	6	4	< 5	448	118	None	
Temperature, water	Degree/Celsis	3	3	25	29	28	None	
Turbidity	NTU	3	3	0.22	5.7	2.3	None	
Nitrate	mg/L	3	3	0.076	0.71	0.46	10	0
E. coli	per 100 mL	9	2	Absent	Present		None	
Sulfur	μg/L	1	1	< 1,000	7,550	2,850	None	
Bromide	mg/L	1	1	0.26	0.26	0.26	None	

[a]Note: not all parameters were analyzed in every sample.

[b]Minimum values: If reports included non-detects of a particular chemical, the minimum value in the table was shown as being less than (<) the lowest laboratory detection limit.

[c]Mean values: Non-detected chemicals were assigned a concentration equal to half of the detection limit *only if* there were other samples that detected the chemical.

[d]MCL: Maximum Contaminant Levels published by the Pennsylvania Department of Environmental Protection Division of Drinking Water Management.

[e]No values are provided if MCLs for substances do not exist.

[f]Two samples had higher acidity (lower pH) than the value recommended by the PA DEP.

Table 5. Match between Health Symptoms Reported by Individuals at Air Testing Sites and Known Effects of Chemicals Detected

County	Number of individuals surveyed at homes where testing was conducted	Match between known health effects of chemicals detected and symptoms reported (percent)[a]	
		Average	Range
Overall	59	68	33-100
Fayette	16	73	33-100
Washington	15	73	33-100
Bradford	8	58	16-100
Butler	8	63	56-68
Bedford	6	69	63-100
Elk	2	64	53-74
Clearfield	1	none	none
Greene	1	70	70
Susquehanna	1	50	50

[a]When a health symptom was associated in the literature with more than one of the chemicals detected, only one match was counted for that symptom.

As mentioned above, levels of iron, manganese, arsenic, and lead were detected in our water well samples in Bradford and Butler Counties at levels that exceeded drinking water standards set by the Pennsylvania DEP. These substances are known to be associated with numerous symptoms reported by individuals living in the homes where these particular exceedances occurred, including symptoms in the categories of sinus/respiratory, skin reactions, digestive/stomach, vision/eyes, ear/nose/mouth, neurological, muscle/joint, behavioral/mood/energy, and liver and kidney damage. Survey participants in the homes where water samples contained methane reported health symptoms known to be associated with methane, including in the categories of sinus/respiratory, digestive/stomach, neurological, and behavioral/mood/energy. While the water samples taken for this project did not show detectable exceedances of safety standards for other substances, it is notable that no drinking water standards have been set for methane, bromide, sodium, strontium, or Total Suspended Solids (TSS)—and thus no exceedances would be indicated in laboratory reports.

Table 6. Percent of Individuals at Air Testing Sites Reporting Symptoms Associated in the Literature with Chemicals Detected at Those Sites, by Symptom Category and Primary Air

		Testing counties					
Symptom category	All	Bedford	Bradford	Butler	Fayette	Washington	Others[a]
Sinus/respiratory	83	100	88	100	81	73	80
Vision/eyes	73	—	100	63	69	67	60
Digestive/stomach	69	50	63	88	75	80	—
Skin reactions	63	50	63	88	69	53	40
Neurological	60	50	88	75	44	53	60
Behavioral/mood/energy	54	67	50	63	63	47	40
Ear/nose/mouth	33	50	—	38	44	33	20
Muscle problems	—	—	—	—	—	40	—

[a]This includes air samples from Clearfield, Elk, Greene, and Susquehanna counties.

DISCUSSION

> Complete evidence regarding health impacts of gas drilling cannot be obtained due to incomplete testing and disclosure of chemicals, and non-disclosure agreements. Without rigorous scientific studies, the gas drilling boom sweeping the world will remain an uncontrolled health experiment on an enormous scale.
>
> —Michelle Bamberger and Robert Oswald [16]

While the survey and testing results, and their related findings, do not constitute definitive proof of cause and effect, we believe they do indicate the strong likelihood that the health of people living in proximity to gas facilities is being affected by exposure to pollutants from those facilities. Most participants report a high number of health symptoms; similar patterns of symptoms were identified across project locations and distances from facilities; and consistency in symptoms reported exists regardless of age group or smoking history. In addition, contaminants that result from oil and gas development were detected in air and water samples in areas where residents are experiencing health symptoms that are established in the literature as consistent with such exposures.

Because of the short-term nature of the air-canister testing (24 hours) and the single water tests conducted at households, our results were contingent on conditions at particular "moments in time." Thus additional chemicals, or the same chemicals at different concentrations, might be captured through expanded testing; and residents could be experiencing exposures that were not detected but would be detectable through such testing. In addition, some of the variation in the air test results may have been due to the different reporting protocols of the laboratories used in this project. Although all the labs test for the same core suite of chemicals, both their reporting limits and the additional chemicals for which they test vary. These will be key considerations for future testing work.

Another consideration that warrants further exploration involves the established standards on both the state and federal levels for "safe" concentrations, which are set only for exposure to single contaminants. This prevailing regulatory approach can not adequately address the potential risks posed by chronic, long-term exposure to lower levels of multiple contaminants simultaneously—in other words, the experience of people living in oil and gas areas day in and day out, and of workers at job sites where toxic substances are continuously used. In addition, for many substances in the environment (including those that come from gas operations and were detected in our air and water sampling), data on health risks or safe exposure levels simply do not exist.

More research is also needed that focuses on the sources of odors and odor events experienced by residents living near gas facilities. In some cases, participants reported different health impacts associated with specific sources and odor events than those they reported in the overall health survey. Since odors are

a clear sign of the presence of airborne substances (such as fuel and chemicals), this aspect warrants tracking and analysis.

Although we did not investigate additional factors that can influence health conditions (e.g., through ordered control groups, in-depth health history research, or identification of other potential sources of contaminants), such factors may affect an individual's health independent of gas operations. The relationship between symptoms and distance from gas facilities also warrants more research.

At the same time, we strongly suggest that for individuals with a history of other health concerns (e.g., asthma or heart conditions) and who are already living with other exposures (e.g., traffic fumes or workplace chemicals), the presence of gas facilities and related pollution could have a strong "trigger effect" that can make existing problems worse and put individuals at higher risk of developing new ones.

RECOMMENDATIONS

As discussed earlier, scientific knowledge about the health and environmental impacts of shale gas development—and also the adoption of policy and regulatory measures to prevent them—are proceeding at a far slower pace than the development itself. This timing mismatch creates situations (already being experienced by residents of Pennsylvania and other states) in which problems are widely reported but left unaddressed. Several measures can be taken to ensure that public health impacts are fully understood and given greater priority in decision-making about shale gas development.

1) *Elevate the role of public health considerations in gas development decisions.* A key measure would be to conduct health impact assessments before permitting begins. HIAs aim to minimize negative impacts and to improve health outcomes associated with land use decisions by analyzing problems that could arise over time, as well as existing health and environmental risks that could be exacerbated by new activities [46]. HIAs can also have a strong preventive effect by identifying mitigation measures related to aspects such as toxic exposures, air and water pollution, and emergency response [47]. In addition, regulatory agencies could comprehensively plan the scope and pace of permits for wells and other facilities in order to reduce impacts on air and water quality, rather than continuing the permit-by-permit process currently being followed in Pennsylvania and other states. Information on where wells and facilities would be built in relation to places where health could be at risk (e.g., homes, schools, and hospitals) could also be required in permit applications.

2) *Increase the involvement of state departments of health in assessing the impacts of gas development.* Efforts should be increased to track and respond to health concerns, and a database should be established to document these problems and the agency response. Health departments could provide training for health and medical professionals on exposure pathways and health symptoms

related to gas operations, so that residents receive more informed advice and appropriate testing and care referrals. Financial aid mechanisms should be established to enable low-income residents to have blood and urine tests for chemical exposure.

3) *Conduct baseline water testing and continuous long-term monitoring of air quality.* Such testing would apply to private wells and public drinking water supplies prior to drilling and to the air at or near facilities during all phases of operations. Testing and monitoring should cover a full suite of chemicals, and contaminants and results should be reported regularly and made available to the public. Air quality testing in particular should be conducted at a range of facilities (e.g., compressor stations, impoundment pits, dehydrators) that cause emissions. These efforts could be carried out by the state regulatory agencies that issue permits or through an agreement between those agencies and health departments. Inter-agency agreements could also be developed to track potential health impacts that could result following spills of chemicals and waste, the underground migration of fracturing fluids, leaks, and other problems.

4) *Strengthen regulations for facilities to minimize air and water pollution risks.* These could include significantly increased setback distances; the installation of advanced technologies on all equipment to reduce emissions, odors, and noise; the use of closed-loop storage systems for waste and drilling fluids (rather than open pits); and the practice of "green completions" to reduce or eliminate flaring and venting of methane gas and other pollutants.

5) *Advance changes in testing parameters that determine "safe" exposure in order to account for low-level, chronic exposure and multiple chemical exposure in testing and monitoring.* Such changes are necessary to reflect impacts on people living in oil and gas development areas day in and day out, as well as workers at facilities. Under current testing parameters (which are based largely on acute episodes involving single contaminants), results may show below-threshold levels even though residents are negatively affected. For example, a recent paper showed that endocrine-disrupting chemicals can have different but still harmful effects at lower doses than at higher ones and concluded that fundamental changes in chemical testing and safety protocols are needed to protect human health [48]. Additionally, current health guidelines should be updated to capture more of the chemicals currently in use and to assess complex or indirect sources of contamination, such as oil and gas operations that rely on a variety of substances, equipment, and facilities at numerous stages of development.

CONCLUSION

> While we realize that human activities may involve hazards, people must proceed more carefully than has been the case in recent history. Corporations, government entities, organizations, communities, scientists, and other individuals must adopt a precautionary approach to all human endeavors. . . . When an activity raises threats of harm to human health or the environment,

> precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.
>
> —Wingspread Consensus Statement on the Precautionary Principle [49]

Across the gas patches of the United States, people experiencing health problems voice the simple wish to be believed. Many say that their health has worsened since gas development began in their communities and that they feel better when they are away from home. Often these conversations turn to what it will take for regulators and policymakers to view their stories not just as "anecdotes," but as valid concerns worthy of an effective response.

There is no doubt that more research on the environmental and health impacts of shale gas development is needed and can play a critical role in making sound decisions about a complex and controversial issue. Yet an equally important consideration is how to respond to the presence of unanswered questions. For many proponents of unfettered gas development, the absence of definitive causal links between gas facilities and specific health impacts indicates the absence of a problem. But for impacted communities and others who believe health and the environment deserve protection and that water and air quality should be maintained, what we don't yet know makes the need for caution even greater.

We believe that the findings of this survey and testing project in Pennsylvania, coupled with similar projects elsewhere and an emerging body of research, provide sufficient evidence for decision-makers to take action to slow the rush to drill, at least until the wide gaps in scientific knowledge, policies, and regulations are bridged. Much is already known about the chemicals used and pollution caused by oil and gas activities, which alone create the real potential for negative health effects in any area where development occurs [50]. The precautionary principle should be applied to decisions about shale gas development (both in existing gas patches and in areas slated for new development), and this should include shifting the burden of proof that harm does or does not occur to those proposing the action.

The status quo—in which science and policy changes proceed slowly while gas development accelerates rapidly—is likely to worsen air and water quality, resulting in negative health impacts and possibly a public health crisis. Greater understanding of the experiences reported by individuals living near gas facilities can play an important role in pointing the way forward to preventing these problems, both in Pennsylvania and nationwide.

ACKNOWLEDGMENTS

This project would not have been possible without the caring, concern, and openness of project participants, who shared their time and personal experiences and trusted us to write about them. Much gratitude is also owed to the community members and organizational partners who provided the contacts and guidance

that made it possible to engage project participants. Many thanks to the Colcom Foundation for its generous support of this project and commitment to protecting the environment and public health.

AUTHORS' BIOGRAPHIES

NADIA STEINZOR is the Eastern Program Coordinator of Earthworks' Oil & Gas Accountability Project. She works with landowners, concerned citizens, and environmental organizations to educate and support impacted communities, advance state oil and gas regulations, and promote Earthworks' federal reform agenda. Nadia has worked for nearly two decades in research, communications, writing, and editing to promote action and policies on environmental protection and land conservation. She holds an M.S. in Environmental Policy from Bard College and an M.A. in Peace and Development Studies from the University of Gothenburg, Sweden. Send email to her at nsteinzor@earthworksaction.org

WILMA SUBRA is President of Subra Company, Inc., a chemistry lab and environmental consulting firm in New Iberia, Louisiana, which provides technical assistance to citizens and victims of environmental issues. She serves on local, state, and federal committees dealing with oilfield waste, oil refineries, and toxic release inventory. Wilma holds an M.S. in Microbiology and Chemistry from the University of Southwestern Louisiana. She is a recipient of the MacArthur Fellowship Genius Award for helping ordinary citizens understand, cope with, and combat environmental problems in their communities. Send email to her at subracom@aol.com

LISA SUMI is a consultant who works on the environmental, community, and health impacts of extractive industries such as coal and hard rock mining, tar sands, and oil and gas. She conducts work that integrates science, technology, policy, and corporate research and analysis with community education and outreach. She has served as Research Director for the Oil and Gas Accountability Project and the Environmental Mining Council of British Columbia, and has worked for clients such as As You Sow, Council of Canadians, Earthworks, ForestEthics, Initiative for Responsible Mining Assurance, Massachusetts Institute of Technology Center for Future Civic Media, MiningWatch Canada, and Natural Resources Defense Council. Lisa holds a M.S. in Physical Geography from the University of Toronto. Send email to her at Isumi@earthworksaction.org

NOTES

1. Institute of Medicine, "The Health Impact Assessment of New Energy Sources: Shale Gas Extraction," www.iom.edu/Activities/Environment/EnvironmentalHealthRT/2012-APR-30.aspx (accessed June 27, 2012).

2. U.S. Energy Information Administration, "Number of Producing Gas Wells," [data table], http://205.254.135.7/dnav/ng/ng_prod_wells_s1_a.htm (accessed July 8, 2012).
3. Pennsylvania Department of Environmental Protection, "Oil and Gas Reports," www.portal.state.pa.us/portal/server.pt/community/oil_and_gas_reports/20297#InteractiveReports (accessed September 10, 2012).
4. C. W. Schmidt, "Blind Rush? Shale Gas Boom Proceeds amid Human Health Questions," *Environmental Health Perspectives* 119 (2011): A348-353, doi: 10.1289/ehp.119-a348.
5. Earthworks Oil and Gas Accountability Project, "Oil and Gas Pollution," www.earthworksaction.org/issues/detail/oil_and_gas_pollution (accessed September 20, 2012).
6. Pennsylvania Alliance for Clean Water and Air, "List of the Harmed," http://pennsylvaniaallianceforcleanwaterandair.wordpress.com/the-list/ (accessed July 8, 2012).
7. Edward Humes, "Fractured Lives: Detritus of Pennsylvania's Shale Gas Boom," *Sierra Magazine,* July/August 2012, 52-59.
8. Earthworks' Oil & Gas Accountability Project, *Natural Gas Flowback: How the Texas Gas Boom Affects Community Health and Safety,* 2011.
9. Earthworks' Oil & Gas Accountability Project, *Health Survey Results of Current and Former Residents of DISH/Clark, Texas Residents*, 2009.
10. Earthworks' Oil & Gas Accountability Project, *Community Health Survey Results: Pavillion, Wyoming,* 2010.
11. Subra Company, *Health Report on Mossville, Calcasieu Parish, Louisiana*, 2009.
12. Louisiana Environmental Action Network, "Survey of the Human Health Impacts Due to the BP Deepwater Horizon Disaster," 2012, http://leanweb.org/our-work/water/bp-oil-spill/results-of-the-louisiana-environmental-action-network-lean-survey-of-the-human-health-impacts-due-to-the-bp-deepwater-horizon-disaster (accessed July 15, 2012).
13. R. Witter et al., *Potential Exposure-Related Human Health Effects of Oil and Gas Development: A Literature Review (2003-2008),* 2008.
14. T. Colborn et al., "Natural Gas Operations from a Public Health Perspective," *Human & Ecological Risk Assessment* 17 (5) (2011): 1039-1056, doi: 10.1080/10807039.2011.605662.
15. L. M. McKenzie et al., "Human Health Risk Assessment of Air Emissions from Development of Unconventional Natural Gas Resources," *Science of the Total Environment* 1 (424) (2012): 79-87, doi: 10.1016/j.scitotenv.2012.02.018.
16. M. Bamberger and R. E. Oswald, "Impacts of Gas Drilling on Human and Animal Health," *New Solutions: A Journal of Environmental and Occupational Health Policy* 22 (1) (2012): 51-77, doi: 10.2190/NS.22.1.e.
17. B. Goldstein, J. Kriesky, and B. Pavliakova, "Missing from the Table: Role of the Environmental Public Health Community in Governmental Advisory Commissions Related to Marcellus Shale Drilling," *Environmental Health Perspectives* 120 (4) (2012): 483-486, doi: 10.1289/ehp.1104594.
18. The Health Impact Project, "HIA in the United States," www.healthimpactproject.org/hia/us (accessed June 27, 2012).
19. U.S. Environmental Protection Agency, "Ambient Air Monitoring Program," http://www.epa.gov/airquality/qa/monprog.html (accessed September 20, 2012).

20. Clean Air Council, "PA DEP Launches Long-term Air Sampling," http://cleanair.org/program/outdoor_air_pollution/marcellus_shale/pa_dep_launches_long_term_air_sampling (accessed September 20, 2012).
21. Geisinger Health System, "Guthrie Health and Geisinger Collaborate on Marcellus Shale Work," https://webapps.geisinger.org/ghsnews/articles/GuthrieHealthand Geisingerc8464.html (accessed September 22, 2012).
22. National Institutes of Environmental Health Sciences, "Shale Gas Workshop Explores Needed Research on Fracking," *Environmental Factor,* June 2012, www.niehs.nih.gov/news/newsletter/2012/6/spotlight-shalegas/index.htm (accessed September 22, 2012).
23. B. L. Allen, "Shifting Boundary Work: Issues and Tensions in Environmental and Health Science in the Case of Grand Bois, Louisiana," *Science as Culture* 13 (12) (2004): 429-448, doi: 10.1080/0950543042000311805.
24. Minkler, M. et al., *Community-Based Participatory Research: A Strategy for Building Health Communities and Promoting Health through Policy Change,* PolicyLink, School of Public Health, University of California Berkeley, 2012.
25. B. A. Israel et al., "Review of Community-Based Research: Assessing Partnership Approaches to Improve Public Health," *Annual Review of Public Health* 19 (1998): 173-202, doi: 10.1146/annurev.publhealth.19.1.173.
26. National Institute of Environmental Health Sciences, "Community-Based Participatory Research in Environmental Health," Request for Applications ES-01-003, January 2001.
27. M. Hendryx et al., "Self-Reported Cancer Rates in Two Rural Areas of West Virginia With and Without Mountaintop Coal Mining," *Journal of Community Health* 37 (4) (2012): 32-327, doi: 10.1007/s10900-011-9448-5.
28. C. M. E. Krogh et al., "WindVOiCe, A Self-Reporting Survey: Adverse Health Effects, Industrial Wind Turbines, and the Need for Vigilance Monitoring," *Bulletin of Science Technology Society* 31 (4) (2011): 334-345, doi: 10.1177/0270467611412551.
29. Mossville Environmental Action Now, Subra, W., and Advocates for Environmental Human Rights, *Industrial Sources of Dioxin Poisoning in Mossville, Louisiana: A Report Based on the Government's Own Data,* 2007.
30. S. Schiffman, "Science of Odors as a Potential Health Issue," *Journal of Environmental Quality* 34 (2005): 129-138, doi: 10.2134/jeq2005.0129.
31. Pennsylvania Department of Environmental Protection, eFacts database, www.ahs2.dep.state.pa.us/eFACTSWeb/criteria_sitesbymuni.aspx (accessed October 3, 2012).
32. FracTracker, Data-Generated Map of the Distribution of Gas Wells across Pennsylvania, www.fractracker.org/maps (accessed October 3, 2012).
33. D. D. Heckathorn, "Respondent-Driven Sampling: A New Approach to the Study of Hidden Populations," *Social Problems* 44 (2c) (1997): 174-199.
34. Department of Psychology, University of California at Davis, "Types of samples," http://psychology.ucdavis.edu/sommerb/sommerdemo/sampling/types.htm (accessed June 25, 2012).
35. Earthworks' Oil & Gas Accountability Project, *Gas Patch Roulette: How Shale Gas Development Risks Public Health in Pennsylvania,* 2012.
36. Swiss Agency for the Environment, Forests, and Landscapes, "National Air Pollutions Monitoring Network," 2001.

37. Pennsylvania Department of Environmental Protection, *Northeastern Pennsylvania Marcellus Shale Short-Term Ambient Air Sampling Report, 2011; Northcentral Pennsylvania Marcellus Shale Short-Term Ambient Air Sampling Report,* 2011; and *Southwestern Pennsylvania Marcellus Shale Short-Term Ambient Air Sampling Report*, 2010.
38. A. E. Ingraffea, *Fluid Migration Mechanisms Due to Faulty Well Design and/or Construction: An Overview and Recent Experiences in the Pennsylvania Marcellus Play*, 2012.
39. Pennsylvania Department of Environmental Protection, Division of Drinking Water Management, "Maximum Contaminant Levels," www.portal.state.pa.us/portal/server.pt?open=18&objID=437830&mode=2 (accessed July 20, 2012).
40. National Science Foundation, "Can Marcellus Shale Development and Healthy Waterways Co-exist?," www.nsf.gov/discoveries/disc_summ.jsp?cntn_id=122543 (accessed October 2, 2012).
41. Pennsylvania State University Extension. "Iron and Manganese in Private Water Systems," http://extension.psu.edu/water/converted-publications/iron-and-manganese-in-private-water-systems (accessed October 2, 2012).
42. E. Boyer et al., The Center for Rural Pennsylvania, Pennsylvania State University, *The Impact of Marcellus Gas Drilling on Rural Drinking Water Supplies,* 2011.
43. T. Banks, "Fluid Rock Interactions Associated with Hydraulic Fracturing and Natural Gas Development," *Global Water Program Magazine,* January 2011, http://globalwater.jhu.edu/index.php/magazine/article/fluid_rock_interactions_associated_with_hydraulic_fracturing_and_natural_ga/ (accessed October 2, 2012).
44. Agency for Toxic Substances and Disease Registry (ATSDR), "Toxicological Profiles," http://www.atsdr.cdc.gov/toxprofiles/index.asp (accessed July 30, 2012).
45. New Jersey Department of Health, "Right to Know Hazardous Substance Fact Sheets," http://web.doh.state.nj.us/rtkhsfs/indexfs.aspx (accessed July 30, 2012).
46. A. Wernham, "Health Impact Assessment for Shale Gas Extraction," www.healthimpactproject.org/resources/health-impact-assessment-for-shale-gas-extraction (accessed July 10, 2012).
47. Garfield County, Colorado, "Battlement Mesa Health Impact Assessment," www.garfield-county.com/environmental-health/battlement-mesa-health-impact-assessment-ehms.aspx (accessed July 10, 2012).
48. L. N. Vandenberg et al., "Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses," *Endocrine Reviews* 33 (3) (2012): 1-78, doi: 10.1210/er.2011-1050.
49. Science and Environmental Health Network, "Wingspread Consensus Statement on the Precautionary Principle," 1998, www.sehn.org/wing.html (accessed July 18, 2012).
50. R. Witter et al., *Potential Exposure-Related Human Health Effects of Oil and Gas Development: A White Paper,* 2008.

Direct reprint requests to:

Nadia Steinzor
Earthworks' Oil & Gas Accountability Project
P.O. Box 149
Willow, NY 12495
e-mail: nsteinzor@earthworksaction.org

Ellen Webb, Sheila Bushkin-Bedient*, Amanda Cheng, Christopher D. Kassotis, Victoria Balise and Susan C. Nagel*

Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations

Abstract: Unconventional oil and gas (UOG) operations have the potential to increase air and water pollution in communities located near UOG operations. Every stage of UOG operation from well construction to extraction, operations, transportation, and distribution can lead to air and water contamination. Hundreds of chemicals are associated with the process of unconventional oil and natural gas production. In this work, we review the scientific literature providing evidence that adult and early life exposure to chemicals associated with UOG operations can result in adverse reproductive health and developmental effects in humans. Volatile organic compounds (VOCs) [including benzene, toluene, ethyl benzene, and xylene (BTEX) and formaldehyde] and heavy metals (including arsenic, cadmium and lead) are just a few of the known contributors to reduced air and water quality that pose a threat to human developmental and reproductive health. The developing fetus is particularly sensitive to environmental factors, which include air and water pollution. Research shows that there are critical windows of vulnerability during prenatal and early postnatal development, during which chemical exposures can cause potentially permanent damage to the growing embryo and fetus. Many of the air and water pollutants found near UOG operation sites are recognized as being developmental and reproductive toxicants; therefore there is a compelling need to increase our knowledge of the potential health consequences for adults, infants, and children from these chemicals through rapid and thorough health research investigation.

***Corresponding authors: Sheila Bushkin-Bedient,** Institute for Health and the Environment 5 University Place Suite A 217, Rensselaer, New York, USA, E-mail: sbushkin@nycap.rr.com; and **Susan C. Nagel:** University of Missouri – Obstetrics, Gynecology and Women's Health Missouri, Illinois, USA, E-mail: nagels@health.missouri.edu
Ellen Webb: Center for Environmental Health, New York, USA
Amanda Cheng: Center for Environmental Health, New York, USA
Christopher D. Kassotis and Victoria Balise: University of Missouri – Biological Sciences, Columbia, Missouri, USA

Keywords: birth defects; impaired fetal growth; infertility; low birth weight; maternal health; spontaneous abortion; unconventional oil and natural gas extraction (UOG) miscarriage.

DOI 10.1515/reveh-2014-0057
Received August 1, 2014; accepted November 5, 2014

Chemicals and wastewater associated with unconventional oil and natural gas (UOG) operations

The rapid rise in unconventional oil and natural gas (UOG) operations that combine directional drilling and hydraulic fracturing (fracking) increases the opportunity for air and water pollution from these processes, with over 15 million Americans living within one mile of UOG operations. UOG operations involve the injection of millions of gallons of water and thousands of gallons of chemicals into the ground under high pressure to liberate oil and gas. More than 750 chemicals are added throughout the UOG process (1). A subset of chemicals is typically used for individual well pads in order to maximize production based on geology and other factors. These chemicals are added for a number of reasons including the following: increasing the viscosity to keep proppants suspended, preventing corrosion and build-up within pipes, helping to dissolve chemicals into fracturing fluids that facilitate the formation of fractures underground, preserving the viability of the fluids during storage, and preventing bacterial growth in fracturing fluids and pipes (1–3). Some fluids return to the surface immediately and some return to the surface over the life of a producing well; these contain the hydraulic fracturing chemicals and also naturally occurring compounds such as radioactive materials, salts, and heavy metals that are liberated from the shale layer (2, 4–7). Industry reports using approximately

13 known or suspected carcinogens (including benzene and acrylamide), known developmental neurotoxicants, and many volatile organic compounds (VOCs) including the BTEX (benzene, toluene, ethylbenzene, and xylene) chemicals, which have numerous associated adverse health outcomes in humans (1).

UOG operations release large amounts of reproductive, immunological, and neurological toxicants, carcinogens as well as endocrine disrupting chemicals (EDCs) into the environment that may negatively affect human health (8). The chemicals used in or produced by UOG have been linked to negative health effects, including adverse reproductive and developmental outcomes in men, women, infants and children. This article will review evidence that adult and early life exposure to chemicals associated with UOG operations can lead to adverse reproductive and developmental health effects in humans, including infertility, miscarriage, impaired fetal growth, low birth weight, preterm birth, and birth defects (9–14). Many of these same reproductive health impacts have also been observed in companion and farm animals living in intensively drilled areas in the United States (15).

Endocrine disrupting chemicals (EDCs)

Hormones are essential for normal health and development. The Endocrine Society defines EDCs as "Any chemical or mixture of chemicals that interferes with any aspect of hormone action" (16). EDCs can interfere with hormone action in a number of ways, but the two most common are through binding to endogenous hormone receptors or altering endogenous hormone concentrations. EDCs can bind to endogenous hormone receptors and activate or repress the normal response; these can also modify endogenous hormone concentrations by altering hormone synthesis or metabolism and clearance. EDCs are often small lipophilic molecules that can dissolve in the plasma membrane and bind to intracellular receptors. Hence, common targets are ligand activated transcription factors in the nuclear receptor superfamily, including estrogen, androgen, glucocorticoid, progesterone, and thyroid hormone receptors. Hormones work at very low concentrations, for example, estrogens stimulate cell proliferation in the part per trillion range; moreover, while typically less potent, EDCs are often present at much higher concentrations than endogenous hormones (17). EDCs can also stimulate nonmonotonic dose responses, that is, effects seen at high doses do not necessarily predict the quantitative and/or qualitative effects seen at low doses (18).

A potential source of exposure to EDCs is through their use in UOG operations. More than 130 fracturing chemicals have been identified as known or potential EDCs, and many others have yet to be assessed due to lack of Chemical Abstract Service numbers and/or proprietary information concerns (1, 8, 19). Kassotis et al. previously assessed the EDC activities of 24 fracturing chemicals on five hormone receptors, reporting antagonist activities for the majority of the chemicals examined (19, 20), the first report of direct receptor activity for many of them (21–26). Additional work found that surface and ground water from fracturing fluid spill sites in Garfield County, Colorado, exhibited higher EDC activities than samples collected outside the active drilling region (19). Adverse reproductive health outcomes associated with EDC exposures are well documented, with reported effects on reproductive organs, body weight, puberty, fertility, and reproductive cancer incidence (27–31).

Wastewater associated with UOG operations

After the drilling and fracturing phase, a portion of the fracturing fluids immediately return to the surface as flowback water. Large volumes of water, which originate from within the shale layer, later comes to the surface throughout the life of the well and is termed "produced water". Residual fracturing chemicals can continue to emerge with produced water in addition to other compounds that are naturally occurring in the bedrock. Some components of fracturing chemicals remain underground and have an unknown fate. After the desired oil and natural gas components have been separated, the remaining flowback and produced water are considered "wastewater", which now contains industrial fracking chemicals plus naturally occurring substances from the shale or coal bed layer. These include heavy metals, salts, minerals and radioactive substances, which escape from their natural underground location along with the oil and natural gas. Recycling of UOG fluids is often employed, however, this practice is limited in frequency because chemicals can become concentrated in these fluids. Ultimately, a large amount of waste is generated. Traditional wastewater treatment does not adequately remove all of these chemicals.

Currently, there are many strategies to dispose of the millions of gallons of wastewater generated by UOG operations, but none are without risks of environmental contamination. UOG wastewater is disposed of in injection disposal wells, landfills, evaporation pits, municipal wastewater treatment plants, direct discharge into

surface water and other miscellaneous uses like spraying onto roads to reduce dust or melt ice on roads (32). Most of these practices can either directly or indirectly aerosolize chemicals or contaminate surface and ground water. The current practice of injecting large volumes of wastewater, under high hydraulic pressure, has been shown to cause increased seismic activity and earthquakes (33, 34). Although the separation of some naturally occurring radioactive elements in fracturing fluids is known to occur at wastewater treatment centers through the co-precipitation of radium with barium and strontium sulfate, the radium still persists in the environment either through incomplete removal from wastewater or as solid waste produced via co-precipitation (35, 36). Thus, radioactive elements like radium (a known carcinogen) will persist in wastewater, in river sediments, and in waste facilities where precipitate and sludge are disposed. Even when disposed of in landfills and other waste facilities, eventual migration or release of leachate into surface and ground water can still occur (37), thus creating another potential mechanism for environmental contamination with these compounds (35, 36).

Potential routes of exposure to UOG chemicals

Human and animal exposure to UOG chemicals can occur through oral routes like eating, through drinking and dermal routes like cleaning and bathing, and via inhalation of airborne contaminants emitted throughout all stages of UOG lifecycle including production (38, 39).

Water

UOG operations can contaminate both surface and ground water (5, 7, 35, 38, 40–47). Routes of contamination include spills during transport to and from well pads, injection of fluids, failure of cement well casings, and from improper treatment and disposal of wastewater (38, 41, 48–50). Spills are commonly reported, occurring in approximately 1% of all Colorado wells in 2013 (51, 52), with subsequent leaching into ground water occurring at some of these locations (45, 53). Gas and heavy metal concentrations increase in drinking water with proximity to natural gas wells (7, 42, 43, 54). In fact, a recent work has suggested that faulty well casings may be the primary source of this contamination (55). The transportation of chemicals and wastewater to and from well pads also contributes to contamination through traffic accidents and equipment failures of tanker trucks (56, 57). Even when wastewater is treated, it is commonly sent to facilities not designed to remove many of the anthropogenic and naturally occurring compounds present (56, 58–60), resulting in elevated downstream concentrations of radium, barium, strontium, benzene, and other compounds (35, 47). Importantly, surface water accounts for two-thirds of all drinking water use (61).

Air

Oil and natural gas production processes contribute numerous contaminants into the air, resulting in elevated concentrations of hydrocarbons, methane, ozone, nitrogen oxides (NO_x), and VOCs like BTEX, alkenes, alkanes, aromatic compounds, and aldehydes (39, 62–75). VOCs are carbon-based chemicals that easily evaporate at ambient temperatures due to high vapor pressure. Many of these can become dangerous if inhaled in large amounts from the ambient air. BTEX chemicals and formaldehyde are just a few of the many VOCs associated with the various stages of UOG operations. Diesel truck exhaust, emissions from drilling rigs and pumps to obtain chemicals released from natural gas wells also produce VOCs (76). The release of VOCs from some of these sources can include BTEX, and can occur during venting, flaring, production, and from leaks due to faulty casings (77). A cluster of wells located in a small area can lead to the significant accumulation of VOCs in the surrounding air (76). Formaldehyde was found in air samples in a drilling dense area in Garfield County in rural western Colorado and near residential sites (78); it can also be produced during the combustion of natural gas (79). Formaldehyde and acetaldehyde can also form from the chemical reaction caused by sunlight interacting with NO_x and VOCs (78). Air emissions around drill sites and compressor stations have been reported to have elevated concentrations of benzene, formaldehyde, hexane, and hydrogen sulfide. In some cases, their concentrations significantly exceeded the Minimal Risk Level of Hazardous Substances (MRL) of the Agency for Toxic Substances and Disease Registry (ATSDR) and were associated with health impacts on residents (80). Table 1 shows a selected list of hazardous substances on the ATSDR MRL list, which coincide with some of the most common air pollutants.

Ground level ozone is a health concern associated with UOG operations. Ground level ozone is a pollutant that forms when NO_x react with VOCs in the presence of sunlight (81). Release of NO_x and VOCs begins with the use of diesel powered equipment during site preparation and emissions from diesel powered equipment, and

Table 1 Selected chemicals from ATSDR Minimal Risk Levels for Hazardous Substances.

Chemical	Exposure Route	A[a]/I[b]/C[c]	MRL	Toxic endpoint
Benzene	Inhalational	A	0.009 ppm[d]	Immuno
	Inhalational	I	0.006 ppm	Immuno
	Inhalational	C	0.003 ppm	Immuno
	Oral	C	0.0005 mg/kg/day	Immuno
				Immuno
Formaldehyde	Inhalational	A	0.04 ppm	Resp
	Inhalational	I	0.03 ppm	Resp
	Inhalational	C	0.008 ppm	Resp
	Oral	I	0.3 mg/kg/day	Gastro
	Oral	C	0.2 mg/kg/day	Gastro
Hexane	Inhalational	C	0.6 ppm	Neuro
Hydrogen sulfide	Inhalational	A	0.07 ppm	Resp
	Inhalational	I	0.02 ppm	Resp
Ethylbenzene	Inhalational	A	5 ppm	Neuro
	Inhalational	I	2 ppm	Neuro
	Inhalational	C	0.06 ppm	Renal
	Oral	I	0.4 mg/kg/day	Hepatic
Toluene	Inhalational	A	1 ppm	Neuro
	Inhalational	C	0.08 ppm	Neuro
	Oral	A	0.8 mg/kg/day	Neuro
	Oral	I	0.02 mg.kg.day	Neuro
Xylenes (mixed)	Inhalational	A	2 ppm	Neuro
	Inhalational	I	0.6 ppm	Neuro
	Inhalational	C	0.05 ppm	Neuro
	Oral	A	1 mg/kg/day	Neuro
	Oral	I	0.4 mg/kg/day	Neuro
	Oral	C	0.2 mg/kg/day	Neuro

[a]A, Acute; [b]I, Intermediate; [c]C, Chronic; [d]ppm, parts per million. These data were last updated on July 12, 2013.
Source: Agency for Toxic Substance and Disease Registry. http://www.atsdr.cdc.gov/mrls/mrllist.asp.

continues through the processes of drilling and extraction using hydraulic fracturing when millions of gallons of water, chemicals and sand are transported to and from the well pads (46). Modeling studies in the Haynesville and Barnett Shales have suggested increased NO_x and ozone levels in UOG regions (82, 83), whereas increases have been measured in active production areas in New Mexico and Wyoming (84, 85).

Health effects associated with chemicals used in UOG operations

Semen quality

Exposure to chemicals associated with UOG operations has been associated with reduced semen quality in men and laboratory animals. Specifically, exposure to BTEX chemicals has been associated with negative impacts on sperm quantity and quality. Exposure to rubber manufacturing workers has been associated with low sperm count, reduced sperm motility, abnormal sperm morphology, and abnormal semen viscosity (OR>14, 9, 27, and 4 respectively) (86). Workers exposed to toluene, xylene, and benzene showed reduced sperm vitality and activity (87). Toluene metabolites may have the ability to directly target the male reproductive organs by initiating oxidative stress mechanisms resulting in damage to the DNA in the testis (88). Chromosomal abnormalities in sperm have also been associated with benzene exposure (89, 90). Formaldehyde has been associated with decreased sperm count, motility, viability and morphology in mice (91). Ethylene glycol ethers have also been associated with lower sperm count in men (92, 93), an endpoint that may, in part, be due to reduced testosterone (94, 95). Ambient ozone has been negatively associated with sperm concentration in men (96) and in rats (97). Taken together, chemicals associated with UOG operations (e.g., benzene, toluene, formaldehyde, ethylene glycol and ozone) have been associated with negative impacts on semen quality, particularly reduced sperm counts.

Menstrual cycle and fecundity

UOG chemicals have been associated with adverse effects on the menstrual cycle and overall fecundity in women. A study in the manufacturing industry suggests ethylene glycols might be a contributing factor to longer menstrual periods in women (98). Benzene and toluene exposure have been associated with abnormal menstrual cycle length in Beijing petrochemical workers (99).

Women exposed to toluene in the printing industry had lower fecundity (100). A two-fold overall reduction in fecundity was found in women working in areas of exposure to toluene in a cross-sectional time to pregnancy study (100). Toluene has been associated with difficulty conceiving, the inability to conceive, as well as premature menopause in women. Women exposed to toluene at work had more difficulty becoming pregnant than did their unexposed co-workers (9), and levels of benzene and toluene measured in breath have been associated with hormone profiles of nonconceptive menstrual cycles (101). In the laboratory, direct adverse effects of BTEX chemicals have been observed on ovarian cell apoptosis, proliferation, and hormone release in animal ovarian cells (102).

Miscarriage and stillbirth

The endocrine etiologies of miscarriage (spontaneous abortion) and stillbirths are not well understood, though they have been associated with exposure to environmental agents. Miscarriage and stillbirth are common disorders, occurring in 15%–20% of human pregnancies (103, 104). These can be caused by placental oxidative stress, degeneration, and a deterioration of placental function known as placental insufficiency (105), all leading to subsequent decreases in oxygen and nutrient transport to the fetus (106). Exposure to heavy metals during pregnancy is associated with increased risks of miscarriage and/or stillbirths. Heavy metals may be routinely mobilized during hydraulic fracturing operations and have been shown to contaminate surface and ground water (7, 35, 107); in some cases (e.g., lead), they are also inadvertent contaminants in fracturing fluids (1).

Specifically, lead exposure is associated with an increased risk of miscarriage and stillbirth (108–112), potentially due to placental rupture (113). Exposure to cadmium has been shown to result in miscarriage and stillbirths in exposed mothers (114–116), potentially through decreased levels of antioxidants or enhanced lipid peroxidation resulting in oxidative stress (115, 116). Arsenic has also been associated with increased risk of miscarriage (117). Animal models have modeled transport of arsenic across the placenta and subsequent distribution and accumulation in the fetal liver and brain (118). Arsenic can cause placental insuffiency through multiple mechanisms like placental dysmorphogenesis (119), inhibition of enzymes and oxidative stress (117, 120) leading to inflammation (121, 122), and disruption of neovasculogenesis leading to aberrant placenta formation (117, 119). Further investigation is needed to evaluate the potential reproductive and developmental effects associated with exposure to heavy metals mobilized by UOG operations.

Meanwhile, exposure to benzene and toluene, commonly used and produced by UOG operations, have been associated with increased risks for miscarriage (9, 101). Women with high exposure to toluene had three to five times the miscarriage rate of those with low exposure (123), and women with occupational benzene exposure have been shown to have an increased rate of miscarriages based on retrospective recall (124). Paternal occupational exposure to toluene and formaldehyde has also been linked to miscarriage in their partners (125, 126).

Direct epidemiological associations between UOG development and miscarriage is lacking, though recent reports have raised concerns about potential effects. The first reported an unusually high rate of miscarriages and stillbirths from Glenwood Springs, Colorado in January 2014 (127). The majority of these cases presented from the Piceance Shale Basin, a densely-drilled UOG region in Western Colorado, though the Colorado Department of Public Health and Environment concluded that no single environmental factor could explain these anomalies (127). The second anecdotally reported an unusually high rate of miscarriages and stillbirths in Vernal, Utah. This region has seen active UOG development since 2005 and also receives substantial wastewater from other states, with recent work reporting elevated ozone concentrations in this area due to UOG activities (128). Researchers are currently investigating potential links between these adverse outcomes and the UOG processes that occur nearby.

Preterm birth and low birth weight

Exposure to chemicals associated with UOG operations is associated with increased risks of low birth weight (LBW) and preterm birth. LBW is defined as an infant birth weight of <2.5 kg (5.5 lbs), and preterm birth is the birth of an infant prior to 37 weeks of pregnancy. Preterm birth occurs in 12%–13% of US pregnancies, and is a leading global cause of perinatal morbidity and mortality (129, 130). Intrauterine growth restriction (IUGR) refers to the

poor growth of an infant in the womb, and is defined as a birth weight in the lowest 10% of normal weights for gestational age (131). Of the four million neonatal deaths that occur each year, at least 60% are due to LBW associated with IUGR and/or preterm birth (132). Several chemicals associated with UOG operations have been associated with negative birth outcomes. Mechanistically, LBW and preterm birth have been associated with reduced fetal estrogen or estrogen action. Smokers are more likely to have LBW babies (133), due, in part, to decreased estrogens from aromatase inhibitors in the smoke (134, 135). LBW has also been associated with exposure to anti-estrogenic polychlorinated biphenyls (PCBs) (136–139).

Particulate matter is one of the most common air pollutants to be linked to adverse birth outcomes. Fine particulate matter has been linked to preterm birth (140–142), IUGR and LBW (11, 143, 144). Particulate matter (PM) is also commonly released into the surrounding air during tight oil and shale gas operations, especially where there are diesel emissions (66). A relationship between NO_x and preterm birth has been observed (12), whereas exposure to NO_x has been linked to reductions in birth weight (145, 146) and IUGR (147). Ozone, another byproduct of UOG operations, has also been linked in a number of studies to LBW and preterm birth (140, 144, 148, 149).

There is an association between air pollution and UOG operations and between air pollution and low birth weight, IUGR and preterm birth. Studies have now begun to assess a more direct link between UOG and adverse fetal outcomes. A preliminary study from the Marcellus Shale region reports increased LBW children from mothers living within 2.5 km of a natural gas well (150). By contrast, a recent work has reported a slight negative association between maternal residence proximity to natural gas wells and preterm birth and LBW (14). The findings from these and other studies indicate that exposure to chemicals from UOG operations (including BTEX, formaldehyde, and ethylene glycols) have the potential to adversely impact male and female fertility, as well as increase rates of miscarriage, preterm birth, and LBW.

Birth defects and developmental origins of health and disease

Maternal exposure to chemicals via inhalation or ingestion of contaminated air, water and foods can adversely affect developing fetuses (151, 152). Most chemicals pass from mother through the placenta to expose the developing embryo and fetus and many chemicals pass from breast milk to baby (152–154). This includes heavy metals, many persistent organic pollutants (POPs), and lipophilic chemicals including aromatic hydrocarbons like BTEX. POPs are characterized by their long half-lives and inability to be metabolized or excreted. These characteristics lead to bioaccumulation in the adipose tissue and result in a persistent "body burden" of hundreds of chemicals. Changes in absorption and metabolism during pregnancy and lactation can liberate chemicals from maternal fat and bone through fat mobilization and demineralization and expose the fetus and infant (155, 156).

McKenzie et al. examined maternal proximity to natural gas wells in rural Colorado and the incidence of three births defects recorded by the state of Colorado. Living within 10 miles of a natural gas well was associated with increased risk of congenital heart and neural tube defects (14). There is a clear potential mechanistic association between UOG chemicals and these birth defects because maternal exposure to chemicals used in UOG processes have been linked to specific birth defects. For example, maternal benzene exposure has been linked to neural tube defects in their children (13, 157). BTEX exposure during the first trimester of pregnancy is negatively associated with biparietal brain diameter between weeks 20 and 32 of pregnancy (158). Maternal EDC exposure has been linked to congenital heart defects, with increased risks for those with polymorphisms in multidrug resistance gene ABCB1 (159).

In addition to birth defects, fetuses and young children are uniquely sensitive to long-term adverse effects from chemical, environmental and nutritional exposures that may not always be apparent at birth. Alterations in the prenatal and postnatal environment can have long-term negative consequences, termed developmental origins of health and disease. Normal development is highly controlled by hormones, and disruption by manmade chemicals can permanently change the course of development. A sentinel example of developmental programming in humans is the use of diethystilbestrol (DES) by pregnant women in the attempt to prevent miscarriage. Later, it was found that maternal DES use increased the risk of reproductive tract abnormalities, vaginal and breast cancer, spontaneous abortion, and stillbirth in DES daughters whose mothers took DES during pregnancy (160, 161). DES sons also experienced long-term negative health impacts. These highlight the fact that some effects from developmental programming by EDCs may not become fully expressed until sexual maturity or even middle age.

The development of the human reproductive system begins during fetal life with sexual differentiation and the development of the reproductive organs. Many chemicals associated with UOG processes are EDCs that can block or antagonize hormone receptors, particularly androgen and

estrogen receptors, termed antiestrogens and antiandrogens, respectively (19). Prenatal exposure to anti-androgenic EDCs like ethylene glycol can lead to delayed sexual development, hypospadias, cryptorchidism, decreased anogenital distance, which is associated with poor semen quality, and other problems (10, 162). Many pesticides have anti-androgenic activity, and a strong association has been found between pesticides and hypospadias (10, 25). Prenatal exposure to ethylene glycol-methyl cellosolve can lead to reproductive damage, congenital birth defects, intrauterine growth restriction and death (163). Perinatal exposure to toluene can reduce serum testosterone in pre- and post-pubertal rats (164). Prenatal exposure to antiestrogenic EDCs has been associated with reduced serum testosterone and elevated FSH in Taiwanese boys whose mothers had been exposed to polychlorinated biphenyls (PCBs) and dibenzofurans (PCDFs) during pregnancy (165). Abnormal menstruation and high FSH serum levels in adolescent girls have been associated with PCBs and PCDEs exposure during prenatal development [reviewed in (166)].

The reproductive tract is not the only target for EDCs during development. Perinatal exposure to EDCs has been shown to cause permanent changes in the brain, behavior, obesity, fertility, cancer and other adverse health outcomes in laboratory animals [reviewed in (18, 167, 168)]. These effects are dependent on the timing of exposure; these are also possibly inherited and passed through epigenetic changes that can be silent for years only to become apparent later (169). Further work should carefully assess the potential for exposure to UOG chemicals and developmental programming as the exposed populations age, particularly in regions like Texas and Colorado, that have experienced UOG production for the longest periods of time.

Conclusions

Exposure to chemical pollution can be linked to reproductive and developmental health impacts including infertility, miscarriage or spontaneous abortion, impaired fetal growth, and LBW. Given that many of the air and water pollutants found near UOG sites are recognized as being developmental and reproductive toxicants, there is a compelling need to increase our knowledge of the potential health consequences for infants, children, and adults from these chemicals through rapid and thorough further health research investigation. Chemicals used and produced in UOG operations are associated with human health effects and demonstrated to cause reproductive and developmental damage in laboratory animals. Whereas environmental human and animal monitoring is needed to measure actual exposure (170), we know enough to know the following:

- There has been and continues to be a dramatic expansion of UOG operations.
- Spills, leaks and discharges of UOG wastewater are common.
- UOG chemicals have been measured in air and water near operations.
- UOG chemicals have been directly linked with adverse reproductive and developmental health outcomes in laboratory studies.
- UOG chemicals have been associated with adverse human reproductive and developmental health outcomes in epidemiological studies.

Taken together, there is an urgent need for the following: 1) biomonitoring of human, domestic and wild animals for these chemicals; and 2) systematic and comprehensive epidemiological studies to examine the potential for human harm.

Literature review

The following peer-reviewed bibliographic databases were used: PubMed, Web of Science, and ScienceDirect, Physicians, Scientists and Engineers for Healthy Energy (PSE) citation database and NYU Erhman Medical Library.

Acknowledgments: Dr. Bushkin-Bedient is sincerely grateful to Erica DeNicola for her invaluable assistance. We also wish to thank Kara Klemp and Chiamaka Isiguzo for help with references. We also wish to thank the Center for Environmental Health (CEH), Concerned Health Professionals of New York and the Institute of Health and the Environment for their support and guidance.

Disclosure: The authors have no relevant financial relationships and no conflicts of interest.

References

1. Committee on Energy and Commerce, Chemicals Used in Hydraulic Fracturing, U.S.H.o. Representatives, Editor. 2011.
2. The Shale Gas Subcommittee of the Secretary of Energy Advisory Board, The SEAB Shale Gas Production Subcommittee Ninety-Day Report. 2011.
3. Riedl J, Rotter S, Faetsch S, Schmitt-Jansen M, Altenburger R. Proposal for applying a component-based mixture approach for

ecotoxicological assessment of fracturing fluids. Environ Earth Sci 2013:1–14.
4. Maule AL, Makey CM, Benson EB, Burrows IJ, Scammell MK. Disclosure of hydraulic fracturing fluid chemical additives: analysis of regulations. New Solut 2013;23(1):167–87.
5. Warner NR, Jackson RB, Darrah T, Osborn SG, Down A, et al. Geochemical evidence for possible natural migration of Marcellus Formation brine to shallow aquifers in Pennsylvania. Proc Natl Acad Sci 2012;109(30):11961–6.
6. Orem W, Tatu C, Varonka M, Lerch H, Bates A, et al. Organic substances in produced and formation water from unconventional natural gas extraction in coal and shale. Int J Coal Geol 2014;126:20–31.
7. Fontenot BE, Hunt LR, Hildenbrand ZL, Carlton Jr DD, Oka H, et al. An evaluation of water quality in private drinking water wells near natural gas extraction sites in the barnett shale formation. Environ Sci Technol 2013;47:10032–40.
8. Colborn T, Kwiatkowski C, Schultz K, Bachran M. Natural gas operations from a public health perspective. Hum Ecol Risk Assess 2011;17(5):1039–56.
9. Attarchi MS, Ashouri M, Labbafinejad Y, Mohammadi S. Assessment of time to pregnancy and spontaneous abortion status following occupational exposure to organic solvents mixture. Int Arch Occup Environ Health 2012;85(3):295–303.
10. Christiansen S, Scholze M, Axelstad M, Boberg J, Kortenkamp A, et al. Combined exposure to anti-androgens causes markedly increased frequencies of hypospadias in the rat. Int J Androl 2008;31(2):241–8.
11. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect 2013;121(3):267–373.
12. Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, et al. Preterm birth and exposure to air pollutants during pregnancy. Environ Res 2010;110(8):778–85.
13. Lupo PJ, Symanski E, Waller DK, Chan W, Langlois PH, et al. Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas, 1999–2004. Environ Health Perspect 2011;119(3):397–402.
14. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, et al. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect 2014;122(4):412–7.
15. Bamberger M. Oswald RE. Impacts of gas drilling on human and animal health. New Solut 2012;22(1):51–77.
16. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society Endocrinology. 2012;153(9):4097–110.
17. Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, et al. Large effects from small exposures I: mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect 2003;111(8):994–1006.
18. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev. 2012;33(3):378–455.
19. Kassotis CD, Tillitt DE, Davis JW, Hormann AM, Nagel SC. Estrogen and androgen receptor activities of hydraulic fracturing chemicals and surface and ground water in a drilling-dense region. Endocrinology 2014;155(3):11.
20. Kassotis CD, Lin C-H, Tillitt D, Nagel SC. Endocrine disrupting activity of hydraulic fracturing chemicals and in vivo adverse health outcomes, in Impacts of Endocrine Disrupting Chemicals on Physiological Functions.MON-0365-MON-0365.
21. Thomas P, Budiantara L. Reproductive life history stages sensitive to oil and naphthalene in atlantic croaker. Marine Environ Res 1995;39:4.
22. Chang H-Y, Shih T-S, Guo YL, Tsai, C-Y, Hsu P-C. Sperm function in workers exposed to N,N-dimethylformamide in the synthetic leather industry. Fertil Steril 2004;81(6):1589–94.
23. Creasy D. A quantitative study of stage-specific spermatocyte damage following administration of ethylene glycol monomethyl ether in the rat. Exp Mol Pathol 1985;43(3):312–36.
24. Devillers J, Chezeau A, Thybaud E, Poulsen V, Porcher J-M, et al. Ecotoxicity of ethylene glycol monobutyl ether and its acetate. Toxicol Mech Method 2002;12:9.
25. Sohoni P, Sumpter JP. Several environmental oestrogens are also anti-androgens. J Endocrinol 1998;158:13.
26. Thayer KA, Belcher SM. Mechanisms of action of bisphenol a and other biochemical/molecular interactions. World Health Organization, 2011.
27. Miao M, Yuan W, Zhu G, He X, Li DK. In utero exposure to bisphenol-A and its effect on birth weight of offspring. Reprod Toxicol 2011;32(1):64–8.
28. Maffini MV, Rubin BS, Sonnenschein C, Soto AM. Endocrine disruptors and reproductive health: the case of bisphenol-A. Mol Cell Endocrinol 2006;254–255:179–86.
29. Pflieger-Bruss S, Schuppe HC, Schill WB. The male reproductive system and its susceptibility to endocrine disrupting chemicals. Andrologia 2004;36(6):337–45.
30. Jacobson-Dickman E, Lee MM. The influence of endocrine disruptors on pubertal timing. Curr Opin Endocrinol Diabetes Obes 2009;16(1):25–30.
31. Eertmans F, Dhooge W, Stuyvaert S, Comhaire F. Endocrine disruptors: effects on male fertility and screening tools for their assessment. Toxicol In Vitro 2003;17(5-6):515–24.
32. Vidic RD, Brantley SL, Vandenbossche JM, Yoxtheimer D, Abad JD. Impact of shale gas development on regional water quality. Science 2013;340(6134):1235009.
33. Ellsworth WL. Injection-induced earthquakes. Science 2013;341(6142):1225942.
34. Holland A. Earthquakes triggered by hydraulic fracturing in South-Central Oklahoma. B Seismol Soc Am 2013;103(3): 1784–92.
35. Alley B, Beebe A, Rodgers Jr J, Castle JW. Chemical and physical characterization of produced waters from conventional and unconventional fossil fuel resources. Chemosphere 2011;85(1):74–82.
36. Zhang T, Gregory K, Hammack RW, Vidic RD. Co-precipitation of radium with barium and strontium sulfate and its impact on the fate of radium during treatment of produced water from unconventional gas extraction. Environ Sci Technol 2014;48(8):4596–603.
37. Masoner JR, Kolpin DW, Furlong ET, Cozzarelli IM, Gray JL, et al. Contaminants of emerging concern in fresh leachate from landfills in the conterminous United States. Environ Sci Process Impacts 2014;16(10):2335–54.

38. Rozell DJ, Reaven SJ. Water pollution risk associated with natural gas extraction from the Marcellus shale. Risk Anal 2012;32(8):1382–93.
39. McKenzie LM, Witter RZ, Newman LS, Adgate JL. Human health risk assessment of air emissions from development of unconventional natural gas resources. Sci Total Environ 2012;424(1):9.
40. DiGiulio DC, Wilkin RT, Miller C, Oberley G. Investigation of ground water contamination near Pavillion. Wyoming, Ada, OK: US Environmental Protection Agency, Office of Research and Development. Report nr EPA 600/R-00/000.
41. Kell S. State oil and gas agency groundwater investigations and their role in advancing regulatory reforms. In: Groundwater Protection Council, editor. A two-state review. Ohio and Texas: Groundwater Protection Council, 2011:165. Available at: http://fracfocus.org/sites/default/files/publications/state_oil__gas_agency_groundwater_investigations_optimized.pdf.
42. Osborn SG, Vengosh A, Warner NR, Jackson RB. Methane contamination of drinking water accompanying gas-well drilling and hydraulic fracturing. Proc Natl Acad Sci USA 2011;108(20):5.
43. Jackson RB, Vengosh A, Darrah TH, Warner NR, Down A, et al. Increased stray gas abundance in a subset of drinking water wells near Marcellus shale gas extraction. Proc Natl Acad Sci USA 2013;110(28):11250–5.
44. Brantley SL, Yoxtheimer D, Arjmand S, Grieve P, Vidic R, et al. Water resource impacts during unconventional shale gas development: The Pennsylvania experience. Int J Coal Geol 2014;126(1):140–56.
45. Gross SA, Avens HJ, Banducci AM, Sahmel J, Panko JM, et al. Analysis of BTEX groundwater concentrations from surface spills associated with hydraulic fracturing operations. J Air Waste Manag Assoc 2013;63(4):424–32.
46. Vengosh A, Jackson RB, Warner N, Darrah TH, Kondash A. A critical review of the risks to water resources from unconventional shale gas development and hydraulic fracturing in the United States. Environ Sci Technol 2014;48(15):8334–48.
47. Ferrar KJ, Michanowicz DR, Christen CL, Mulcahy N, Malone SL, et al. Assessment of effluent contaminants from three facilities discharging Marcellus Shale wastewater to surface waters in Pennsylvania. Environ Sci Technol 2013;47(7):3472–81.
48. Korfmacher KS, Jones WA, Malone SL, Vinci LF. Public health and high volume hydraulic fracturing. New Solut 2013;23(1):13–31.
49. Mauter MS, Alvarez PJ, Burton A, Cafaro DC, Chen W, et al. Regional variation in water-related impacts of shale gas development and implications for emerging international plays. Environ Sci Technol 2014;48(15):8298–306.
50. Ingraffea AR, Wells MT, Santoro RL, Shonkoff SB. Assessment and risk analysis of casing and cement impairment in oil and gas wells in Pennsylvania, 2000–2012. Proc Natl Acad Sci USA 2014;111(30):10955–60.
51. Colorado Oil & Gas Conservation Commission, Colorado Oil and Gas Information System (COGIS). 2014. Available at: http://cogcc.state.co.us/.
52. Colorado Oil & Gas Conservation Commission. Conservation Commission Colorado Weekly and Monthly Oil & Gas Statistics. 2012. (cited 2012 May 15, 2012); 5/7/12: Available at: http://www.colorado.gov/cogcc.
53. Ziemkiewicz PF, Quaranta JD, Darnell A, Wise R. Exposure pathways related to shale gas development and procedures for reducing environmental and public risk. J Nat Gas Sci Eng 2014;16:8.
54. Li H, Carlson KH. Distribution and origin of groundwater methane in the wattenberg oil and gas field of Northern Colorado. Environ Sci Technol 2014;48(3):1484–91.
55. Darrah TH, Vengosh A, Jackson RB, Warner NR, Poreda RJ. Noble gases identify the mechanisms of fugitive gas contamination in drinking-water wells overlying the Marcellus and Barnett Shales. Proc Natl Acad Sci USA 2014;111(39):14076–81.
56. Gilmore KR, Hupp RL, Glathar J. Transport of hydraulic fracturing water and wastes in the Susquehanna River Basin, Pennsylvania. J Environ Eng 2014;140(5):10.
57. Burton Jr GA, Basu N, Ellis BR, Kapo KE, Entrekin S, et al. Hydraulic "fracking": are surface water impacts an ecological concern? Environ Toxicol Chem 2014;33(8):1679–89.
58. Braga O, Smythe GA, Schafer AI, Feitz AJ. Steroid estrogens in primary and tertiary wastewater treatment plants. Water Sci Technol 2005;52(8):273–8.
59. Westerhoff P, Yoon Y, Snyder S, Wert E. Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. Environ Sci Technol 2005;39:15.
60. Campbell C, Borglin S, Green F, Grayson A, Wozei E, et al. Biologically directed environmental monitoring, fate, and transport of estrogenic endocrine disrupting compounds in water: a review. Chemosphere 2006;65(8):1265–80.
61. US Environmental Protection Agency Office of Water, Drinking Water and Ground Water Statistics for 2008, in Report nr EPA 816-K-08-004. 2008: Available at: http://www.epa.gov/ogwdw/databases/pdfs/data_factoids_2008.pdf.
62. Roy AA, Adams PJ, Robinson AL. Air pollutant emissions from the development, production, and processing of Marcellus Shale natural gas. J Air Waste Manag Assoc 2014;64(1):20.
63. Colborn T, Schultz K, Herrick L, Kwiatkowski C. An exploratory study of air quality near natural gas operations. Hum Ecol Risk Assess 2014;20(1):20.
64. Pétron G, Frost G, Miller BR, Hirsch AI, Montzka SA, et al. Hydrocarbon emissions characterization in the Colorado Front Range: a pilot study. J Geophys Res 2012;117:19.
65. Steinzor N, Subra W, Sumi L. Investigating links between shale gas development and health impacts through a community survey project in Pennsylvania. New Solut 2013;23(1):29.
66. Moore CW, Zielinska B, Petron G, Jackson RB. Air impacts of increased natural gas acquisition, processing and use: a critical review. Environ Sci Technol 2014;48(15):8349–59. Available at: http://sites.biology.duke.edu/jackson/est2014a.pdf.
67. Brown D, Weinberger B, Lewis C, Bonaparte H. Understanding exposure from natural gas drilling puts current air standards to the test. Rev Environ Health 2014;29:277–92.
68. Helmig D, Thompson C, Evans J, Park JH. Highly elevated atmospheric levels of volatile organic compounds in the Uintah Basin, Utah. Environ Sci Technol 2014;48(9):4707–15.
69. Sommariva R, Blake RS, Cuss RJ, Cordell RL, Harrington JF, et al. Observations of the release of non-methane hydrocarbons from fractured shale. Environ Sci Technol 2014;48(15):8891–6.
70. Miller SM, Wofsy SC, Michalak AM, Kort EA, Andrews AE, et al. Anthropogenic emissions of methane in the United States. Proc Natl Acad Sci USA 2013;110(50):20018–22.
71. Howarth RW, Santoro R, Ingraffea A. Methane and the greenhouse-gas footprint of natural gas from shale formations. Climatic Change 2011;106:12.

72. Allen DT, Torres VM, Thomas J, Sullivan DW, Harrison M, et al. Measurements of methane emissions at natural gas production sites in the United States. Proc Natl Acad Sci USA 2013;110(44):17768–73.
73. Howarth RW. A bridge to nowhere: methane emissions and the greenhouse gas footprint of natural gas. Energy Sci Eng 2014;1:14.
74. Karion A, Sweeney C, Petron G, Frost G, Hardesty RM, et al. Methane emissions estimate from airborne measurements over a western United States natural gas field. Geophys Res Lett 2013;40:1–5.
75. Jackson RB, Down A, Phillips NG, Ackley RC, Cook CW, et al. Natural gas pipeline leaks across Washington, DC. Environ Sci Technol 2014;48(3):2051–8.
76. Gilman JB, Lerner BM, Kuster WC, de Gouw JA. Source signature of volatile organic compounds from oil and natural gas operations in northeastern Colorado. Environ Sci Technol 2013;47(3):1297–305.
77. Bar-Ilan A, Friesen R, Grant J, Pollack A, Henderer D, et al. Development of Baseline 2006 Emissions from Oil and Gas Activity in Denver-Julesberg Basin. Prepared for the Western Governors' Association by ENVIRON International Corp Novato, CA, 2008,. Available at: http://www.epa.gov/ttnchie1/conference/ei17/session2/amnon.pdf.
78. Colborn T, Schultz K, Herrick L, Kwiatkowski C. An exploratory study of air quality near natural gas operations. Hum Ecol Risk Assess 2013;20(1):86–105.
79. Zhang H, Li J, Ying Q, Guven B, Olaguer E. Source apportionment of Formaldehyde during Texas AQS 2006 using a source-oriented chemical transport model. J GeophysRes Atmos 2006;118(3):1525–35.
80. Macey GP, Breech R, Chernaik M, Cox C, Larson D, et al. Air concentrations of volatile compounds near oil and gas production: a community-based exploratory study. Environ Health 2014;13:82.
81. Pleijel H, Danielsson H, Karlsson GP, Gelang J, Karlsson PE, et al. An ozone flux-response relationship for wheat. Environ Pollut 2000;109(3):453–62.
82. Kemball-Cook S, Bar-Ilan A, Grant J, Parker L, Jung J, et al. Ozone impacts of natural gas development in the Haynesville Shale. Environ Sci Technol 2010;44(24):9357–63.
83. Olaguer EP. The potential near-source ozone impacts of upstream oil and gas industry emissions. J Air Waste Manag Assoc 2012;62(8):966–77.
84. Rodriguez MA, Barna MG, Moore T. Regional impacts of oil and gas development on ozone formation in the western United States. J Air Waste Manag Assoc 2009;59(9):1111–8.
85. Schnell RC, Oltmans SJ, Neely RR, Endres MS, Molenar JV, et al. Rapid photochemical production of ozone at high concentrations in a rural site during winter. Nat Geosci 2009;2:120–2.
86. De Celis R, Feria-Velasco A, Gonzalez-Unzaga M, Torres-Calleja J, Pedron-Nuevo N. Semen quality of workers occupationally exposed to hydrocarbons. Fertil Steril 2000;73(2):221–8.
87. Xiao G, Pan C, Cai Y, Lin H, Fu Z. Effect of benzene, toluene, xylene on the semen quality and the function of accessory gonad of exposed workers. Ind Health 2001;39(2):206–10.
88. Nakai N, Murata M, Nagahama M, Hirase T, Tanaka M, et al. Oxidative DNA damage induced by toluene is involved in its male reproductive toxicity. Free Radic Res 2003;37(1):69–76.
89. Xing C, Marchetti F, Li G, Weldon RH, Kurtovich E, et al. Benzene exposure near the U.S. permissible limit is associated with sperm aneuploidy. Environ Health Perspect 2010;118(6):833–9.
90. Marchetti F, Eskenazi B, Weldon RH, Li G, Zhang L, et al. Occupational exposure to benzene and chromosomal structural aberrations in the sperm of Chinese men. Environ Health Perspect 2012;120(2):229–34.
91. Vosoughi S, Khavanin A, Salehnia M, Asilian Mahabadi H, Shahverdi A, et al. Adverse effects of formaldehyde vapor on mouse sperm parameters and testicular tissue. Int J Fertil Steril 2013;6(4):250–67.
92. Veulemans H, Steeno O, Masschelein R, Groeseneken D. Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case-control study. Br J Ind Med 1993;50(1):71–8.
93. Welch LS, Schrader SM, Turner TW, Cullen MR. Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. Am J Ind Med 1988;14(5):509–26.
94. Svensson BG, Nise G, Erfurth EM, Nilsson A, Skerfving S. Hormone status in occupational toluene exposure. Am J Ind Med 1992;22(1):99–107.
95. Svensson BG, Nise G, Erfurth EM, Olsson H. Neuroendocrine effects in printing workers exposed to toluene. Br J Ind Med 1992;49(6):402–8.
96. Bonde JP. Ozone and semen quality. Environ Health Perspect 2007;115(4):A185; author reply A185–6.
97. Jedlinska-Krakowska M, Gizejewski Z, Dietrich GJ, Jakubowski K, Glogowski J, et al. The effect of increased ozone concentrations in the air on selected aspects of rat reproduction. Pol J Vet Sci 2006;9(1):11–6.
98. Hsieh GY, Wang JD, Cheng TJ, Chen PC. Prolonged menstrual cycles in female workers exposed to ethylene glycol ethers in the semiconductor manufacturing industry. Occup Environ Med 2005;62(8):510–6.
99. Ekpenyong CE, Davies K, Daniel N. Effects of gasoline inhalation on menstrual characteristics and the hormonal profile of female petrol pump workers. J Environ Prot 2013;4:65–73.
100. Plenge-Bonig A, Karmaus W. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. Occup Environ Med 1999;56(7):443–8.
101. Reutman SR, LeMasters GK, Knecht EA, Shukla R, Lockey JE, et al. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. Environ Health Perspect 2002;110(8):805–11.
102. Sirotkin AV, Kádasi A, Baláži A, Baková Z, Harrath AH, et al. Influence of petrochemical industry environmental contaminants on animal ovarian cells. J Microb Biotech Food Sci 2012;2(2):517–25.
103. Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: Involvement of oxidative stress and implications in human evolution. Hum Reprod Update 2006;12(6):747–55.
104. Reddy UM, Laughon SK, Sun L, Troendle J, Willinger M, et al. Prepregnancy risk factors for antepartum stillbirth in the United States. Obstet Gynecol 2010;116(5):1119–26.
105. Gagnon R. Placental insufficiency and its consequences. Eur J Obstet Gynecol Reprod Biol 2003;110(Suppl 1):S99–107.
106. Baschat AA. Fetal responses to placental insufficiency: an update. Br J Obstet Gynecol 2004;111(10):1031–41.
107. Stringfellow WT, Domen JK, Camarillo MK, Sandelin WL, Borglin S. Physical, chemical, and biological characteristics of compounds used in hydraulic fracturing. J Hazard Mater 2014;275:37–54.

108. Baghurst PA, Robertson EF, Oldfield RK, King BM, McMichael AJ, et al. Lead in the placenta, membranes, and umbilical cord in relation to pregnancy outcome in a lead-smelter community. Environ Health Perspect 1991;90:315–20.
109. Bellinger DC. Teratogen update: lead and pregnancy. Birth Defects Res A Clin Mol Teratol 2005;73(6):409–20.
110. Chalupka S, Chalupka AN. The impact of environmental and occupational exposures on reproductive health. J Obstet Gynecol Neonatal Nurs 2010;39(1):84–100; quiz 100-2.
111. Gundacker C, Frohlich S, Graf-Rohrmeister K, Eibenberger B, Jessenig V, et al. Perinatal lead and mercury exposure in Austria. Sci Total Environ 2010;408(23):5744–9.
112. Flora S, Pachauri V, Saxena G. Arsenic, cadmium and lead. Reproductive and developmental toxicology. London: Academic Press, 2011:416–38.
113. Fahim MS, Fahim Z, Hall DG. Effects of subtoxic lead levels on pregnant women in the state of Missouri. Res Commun Chem Pathol Pharmacol 1976;13(2):309–31.
114. Godt J, Scheidig F, Grosse-Siestrup C, Esche V, Brandenburg P, et al. The toxicity of cadmium and resulting hazards for human health. J Occup Med Toxicol 2006;1:22.
115. Saad AA, Hegazy NM, Amer N, Gaber K, Youssef AI, et al. The role of cadmium exposure on spontaneous abortion. World J Med Sci 2012;7(4):6.
116. Thompson J, Bannigan J. Cadmium: toxic effects on the reproductive system and the embryo. Reprod Toxicol 2008;25(3):304–15.
117. Vahter M. Effects of arsenic on maternal and fetal health. Annu Rev Nutr 2009;29:381–99.
118. Jin Y, Xi S, Li X, Lu C, Li G, et al. Arsenic speciation transported through the placenta from mother mice to their newborn pups. Environ Res 2006;101(3):349–55.
119. He W, Greenwell RJ, Brooks DM, Calderon-Garciduenas L, Beall HD, et al. Arsenic exposure in pregnant mice disrupts placental vasculogenesis and causes spontaneous abortion. Toxicol Sci 2007;99(1):244–53.
120. Kumagai Y, Sumi D. Arsenic: signal transduction, transcription factor, and biotransformation involved in cellular response and toxicity. Annu Rev Pharmacol Toxicol 2007;47:243–62.
121. van den Hooven EH, de Kluizenaar Y, Pierik FH, Hofman A, van Ratingen SW, et al. Chronic air pollution exposure during pregnancy and maternal and fetal C-reactive protein levels: the Generation R Study. Environ Health Perspect 2012;120(5):746–51.
122. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. PLoS Genet 2007;3(11):e207.
123. Bukowski JA. Review of the epidemiological evidence relating toluene to reproductive outcomes. Regul Toxicol Pharmacol 2001;33(2):147–56.
124. Xu X, Cho SI, Sammel M, You L, Cui S, et al. Association of petrochemical exposure with spontaneous abortion. Occup Environ Med 1998;55(1):31–6.
125. Taskinen H, Anttila A, Lindbohm ML, Sallmen M, Hemminki K. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. Scand J Work Environ Health 1989;15(5):345–52.
126. Wang HX, Zhou DX, Zheng LR, Zhang J, Huo YW, et al. Effects of paternal occupation exposure to formaldehyde on reproductive outcomes. J Occup Environ Med 2012;54(5):518–24.
127. Colorado Department of Public Health and Environment. Glenwood Springs Prenatal Report, April 2014. State of Colorado, 2014. Available at: http://www.colorado.gov/cs/Satellite?blobcol=urldata&blobheadername1=Content-Disposition&blobheadername2=Content-Type&blobheadervalue1=inline;+filename%3D%22Glenwood+Springs+Prenatal+Report.pdf%22&blobheadervalue2=application/pdf&blobkey=id&blobtable=MungoBlobs&blobwhere=1251979207926&ssbinary=true.
128. Edwards PM, Brown SS, Roberts JM, Ahmadov R, Banta RM, et al. High winter ozone pollution from carbonyl photolysis in an oil and gas basin. Nature 2014;514(7522):351–4.
129. Simmons LE, Rubens CE, Darmstadt GL, Gravett MG. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. Semin Perinatol 2010;34(6):408–15.
130. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371(9606):75–84.
131. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol 2012;10:49.
132. Lawn JE, Cousens S, Zupan J. Lancet Neonatal Survival Steering T. 4 million neonatal deaths: when? where? why? Lancet 2005;365(9462):891–900.
133. Petridou E, Panagiotopoulou K, Katsouyanni K, Spanos E, Trichopoulos D. Tobacco smoking, pregnancy estrogens, and birth weight. Epidemiol 1990;1(3):247–50.
134. Kitawaki J, Inoue S, Tamura T, Yamamoto T, Honjo H, et al. Cigarette smoking during pregnancy lowers aromatase cytochrome P-450 in the human placenta. J Steroid Biochem Mol Biol 1993;45(6):485–91.
135. Osawa Y, Tochigi B, Tochigi M, Ohnishi S, Watanabe Y, et al. Aromatase inhibitors in cigarette smoke, tobacco leaves and other plants. J Enzyme Inhib 1990;4(2):187–200.
136. Baibergenova A, Kudyakov R, Zdeb M, Carpenter DO. Low birth weight and residential proximity to PCB-contaminated waste sites. Environ Health Perspect 2003;111(10):1352–7.
137. Rylander L, Stromberg U, Dyremark E, Ostman C, Nilsson-Ehle P, et al. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. Am J Epidemiol 1998;147(5):10.
138. Calo M, Alberghina D, Bitto A, Lauriano ER, Lo Cascio P. Estrogenic followed by anti-estrogenic effects of PCBs exposure in juvenil fish (Spaurus aurata). Food Chem Toxicol 2010;48(8-9):2458–63.
139. Connor K, Ramamoorthy K, Moore M, Mustain M, Chen I, et al. Hydroxylated polychlorinated biphenyls (PCBs) as estrogens and antiestrogens: structure-activity relationships. Toxicol Appl Pharmacol 1997;145(1):111–23.
140. Hansen C, Neller A, Williams G, Simpson R. Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia. Br J Obstet Gynecol 2006;113(8):935–41.
141. Huynh M, Woodruff TJ, Parker JD, Schoendorf KC. Relationships between air pollution and preterm birth in California. Paediatr Perinat Epidemiol 2006;20(6):454–61.
142. Suh YJ, Kim H, Seo JH, Park H, Kim YJ, et al. Different effects of PM10 exposure on preterm birth by gestational period estimated from time-dependent survival analyses. Int Arch Occup Environ Health 2009;82(5):613–21.
143. Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, et al. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global

survey on maternal and perinatal health. Environ Health Perspect 2014;122(4):425–30.
144. Morello-Frosch R, Jesdale BM, Sadd JL, Pastor M. Ambient air pollution exposure and full-term birth weight in California. Environ Health 2010;9:44.
145. Darrow LA, Klein M, Strickland MJ, Mulholland JA, Tolbert PE. Ambient air pollution and birth weight in full-term infants in Atlanta, 1994–2004. Environ Health Perspect 2011;119(5):731–7.
146. Savitz DA, Bobb JF, Carr JL, Clougherty JE, Dominici F, et al. Ambient fine particulate matter, nitrogen dioxide, and term birth weight in New York, New York. Am J Epidemiol 2014;179(4):457–66.
147. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. Environ Health Perspect 2003;111(14):1773–8.
148. Olsson D, Mogren I, Forsberg B. Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. Br Med J Open 2013;3(2):1–8.
149. Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, et al. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ Health Perspect 2005;113(11):1638–44.
150. Hill EL. Shale gas development and infant health: evidence from Pennsylvania. Working Paper, 2013, Revision December 2013.
151. Barr DB, Bishop A, Needham LL. Concentrations of xenobiotic chemicals in the maternal-fetal unit. Reprod Toxicol 2007;23(3):260–6.
152. Needham LL, Grandjean P, Heinzow B, Jorgensen PJ, Nielsen F, et al. Partition of environmental chemicals between maternal and fetal blood and tissues. Environ Sci Technol 2011;45(3):1121–6.
153. Landrigan PJ, Sonawane B, Mattison D, McCally M, Garg A. Chemical contaminants in breast milk and their impacts on children's health: an overview. Environ Health Perspect 2002;110(6):A313–5.
154. Sonawane BR. Chemical contaminants in human milk: an overview. Environ Health Perspect 1995;103(5):197–205.
155. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 1993;101(5):378–84.
156. Hackley B, Feinstein A, Dixon J. Air pollution: impact on maternal and perinatal health. J Midwifery Womens Health 2007;52(5):435–43.
157. Ruckart PZ, Bove FJ, Maslia M. Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case-control study. Environ Health 2013;12:104.
158. Aguilera I, Garcia-Esteban R, Iniguez C, Nieuwenhuijsen MJ, Rodriguez A, et al. Prenatal exposure to traffic-related air pollution and ultrasound measures of fetal growth in the INMA Sabadell cohort. Environ Health Perspect 2010;118(5):705–11.
159. Wang C, Xie L, Zhou K, Zhan Y, Li Y, et al. Increased risk for congenital heart defects in children carrying the ABCB1 Gene C3435T polymorphism and maternal periconceptional toxicants exposure. PLoS One 2013;8(7):e68807.
160. Herbst AL, Hubby MM, Blough RR, Azizi F. A comparison of pregnancy experience in DES-exposed and DES-unexposed daughters. J Reprod Med 1980;24(2):62–9.
161. Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. N Engl J Med 2011;365(14):1304–14.
162. Mendiola J, Stahlhut RW, Jorgensen N, Liu F, Swan SH. Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York. Environ Health Perspect 2011;119(7):958–63.
163. Arteaga-Martínez M, García-Peláez I, Aguirre-Luna O, Saavedra-Ontiveros D. Teratogenic effect of ethylene glycol-methyl cellosolve mixture in rats: i. reproductive damage. Int J Morphol 2010;28(4):1173–80.
164. Hansson T, Pettersson BM, Eneroth P, Gustafsson JA. Neonatal exposure to toluene: effects on the development of liver microsomal cytochrome P-450 and serum hormone levels in the rat. Toxicology 1985;37(1-2):39–50.
165. Hsu JF, Guo YL, Yang SY, Liao PC. Congener profiles of PCBs and PCDD/Fs in Yucheng victims fifteen years after exposure to toxic rice-bran oils and their implications for epidemiologic studies. Chemosphere 2005;61(9):1231–43.
166. Leijs MM, van der Linden LM, Koppe JG, Olie K, van Aalderen WM, et al. The influence of perinatal and current dioxin and PCB exposure on reproductive parameters (sex-ratio, menstrual cycle characteristics, endometriosis, semen quality, and prematurity): a review. Biomonitoring 2014;1(1):1–15.
167. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30(4):293–342.
168. Vandenberg LN. Low-dose effects of hormones and endocrine disruptors. Vitam Horm 2014;94:129–65.
169. Zama AM, Uzumcu M. Epigenetic effects of endocrine-disrupting chemicals on female reproduction: an ovarian perspective. Front Neuroendocrinol 2010;31(4):420–39.
170. Penning TM, Breysse PN, Gray K, Howarth M, Yan B. Environmental health research recommendations from the inter-environmental health sciences core center working group on unconventional natural gas drilling operations. Environ Health Perspect 2014;122(11):1155–9.