EPA Science Advisory Board
Hydraulic Fracturing Research Advisory Panel
Public Teleconference February 1, 2016
Oral Statement of Carol Kwiatkowski

From: Carol Kwiatkowski
Sent: Wednesday, February 03, 2016 12:19 PM
To: Hanlon, Edward <Hanlon.Edward@epa.gov>
Cc: 'Jeff Zimmerman'
Subject: Written comments for the EPA Science Advisory Board Hydraulic Fracturing Research Advisory Panel

Dear Mr. Hanlon,

Attached is a copy of the oral statement I delivered on Monday to the EPA Science Advisory Board Hydraulic Fracturing Research Advisory Panel. I was told that the SAB requested to see the studies I referenced, so I have cited them in the written testimony and attached them as PDFs for the panel members. I would appreciate a reply indicating that the panel has received my testimony and the studies. Many thanks for your help in this matter.
Carol

Carol F. Kwiatkowski, PhD
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TEDX

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To: Mr. Edward Hanlon, Environmental Protection Agency Designated Federal Officer

Re: Written statement of oral comments presented February 1, 2016 to the EPA Science Advisory Board Hydraulic Fracturing Research Advisory Panel

Date: February 3, 2016

Thank you for this opportunity to share new scientific information with the Science Advisory Board.

I'm Dr. Carol Kwiatkowski, Executive Director of The Endocrine Disruption Exchange, known as TEDX. TEDX is a non-profit organization whose mission is to educate people on the health and environmental impacts of chemical exposure. I am also an adjunct faculty member at the University of Colorado, Boulder. I am an author on three scientific articles on natural gas development, one of which is under review.

On the TEDX website we have a reference list of 48 peer-reviewed articles published since 2009 related to health impacts of unconventional oil and gas http://endocrinedisruption.org/chemicals-in-natural-gas-operations/peer-reviewed-articles. Some are very new and I want to highlight them for you today, particularly as they are related to reproduction, development, and hormone activity.

One study, published this year, evaluated the potential reproductive and developmental toxicity of 240 chemicals in fracking fluids and wastewater. Sixty-five percent were shown to affect reproduction, development, or both (Elliott, Ettinger et al. 2016). This corroborates work we published in 2011 (Colborn, Kwiatkowski et al. 2011).

Further, in a recent *in vitro* study, out of 24 oil and gas related chemicals tested, 23 had hormone activity. When a mixture of these hormonally active chemicals was given to pregnant mice, their male offspring had decreased sperm, increased serum testosterone, and increased organ weights (Kassotis, Klemp et al. 2015). Research has also demonstrated the presence of these chemicals in surface and ground water near oil and gas development (Kassotis, Tillitt et al. 2014). It's

important to mention that chemicals that disrupt hormone function can do so at extremely low concentrations.

With regard to human evidence, several studies conducted by scientists at the University of Colorado describe possible, probable and actual health impacts of living near oil and gas development. The most striking of these was a study of 125K birth records from 57 rural Colorado counties (McKenzie, Guo et al. 2014). It revealed that pregnant women living near oil and gas development were more likely to give birth to babies with congenital heart defects.

Two other similar studies were published in 2015. One was conducted in Southwest Pennsylvania by scientists at the University of Pittsburgh studying over 15,000 birth records. Babies born near more wells had a greater likelihood of being born small for gestational age and had significantly lower birth weights (Stacy, Brink et al. 2015). Being born underweight has been linked to heart disease, diabetes, and childhood asthma.

The other study was conducted in Central and Northeast Pennsylvania by scientists at Johns Hopkins University, studying over 10,000 birth records. They found proximity to oil and gas development to be associated with an increased likelihood of high-risk pregnancy in the mothers, and preterm birth in the babies (Casey, Savitz et al. 2015).

The important points here are that data from tens of thousands of pregnant women and babies were analyzed in these studies, which were conducted in three different regions of the country, by independent scientists. We don’t know if the health effects are from air or water exposure. What we do know is that this kind of industrial activity near people’s homes is associated with adverse outcomes in two very vulnerable populations – pregnant women, and children developing in the womb.

There is simply no logic in waiting for widespread systemic impacts to be proven. The finding that hydraulic fracturing can and has contaminated drinking water should be the finding that triggers protective action. So I am urging you to act quickly to correct and finalize the EPA report, as people, including pregnant women and children, continue to be exposed to these chemicals.

Thank you.

Carol F. Kwiatkowski
Executive Director, TEDX

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PLOS | ONE

RESEARCH ARTICLE

Perinatal Outcomes and Unconventional Natural Gas Operations in Southwest Pennsylvania

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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

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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 ith 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 (8th grade or less; 9th-12th 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,

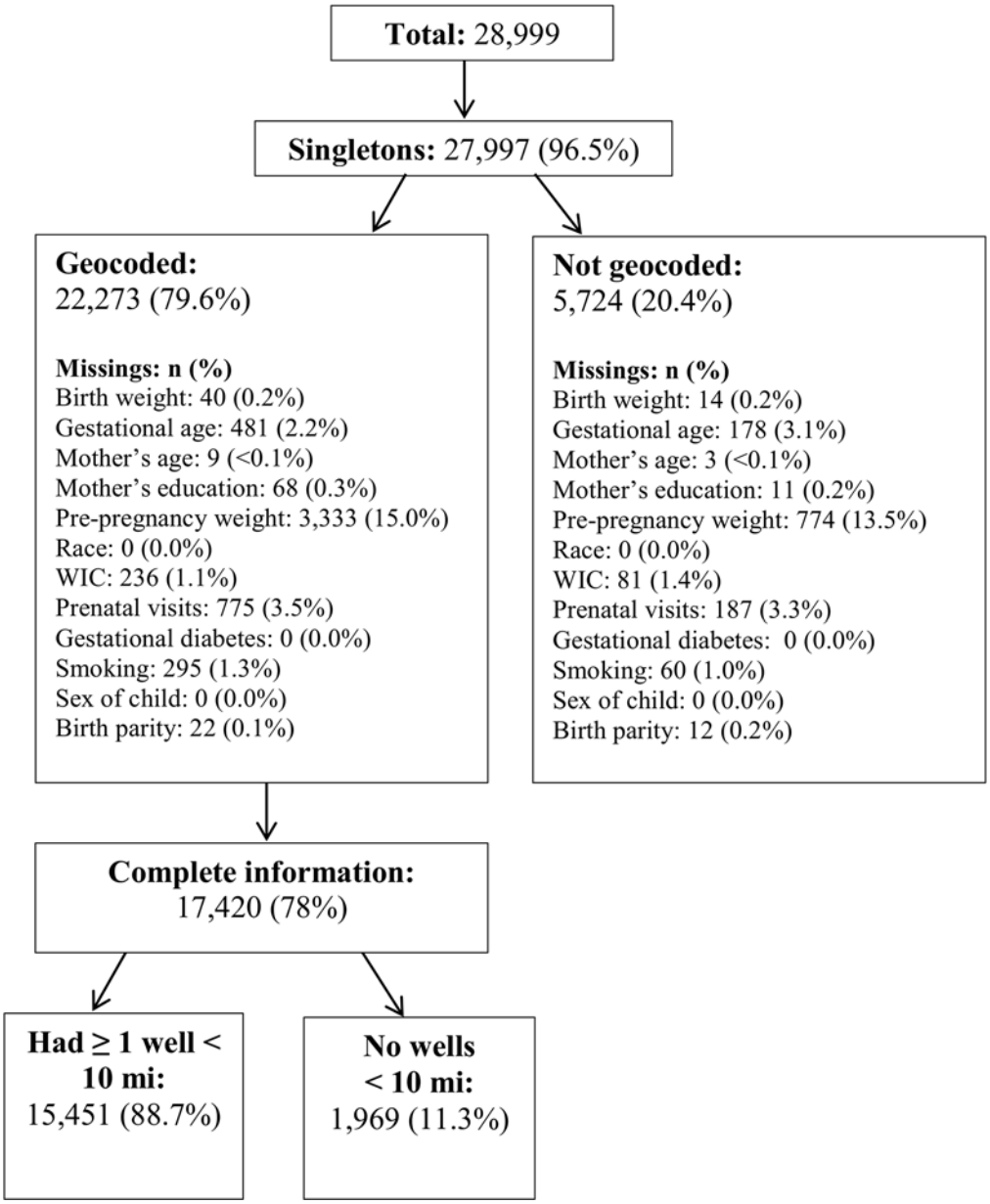

Fig 1. Flowchart of sample sizes and missing data for births in Butler, Washington, and Westmoreland Counties 2007–2010.

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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).

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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.

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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

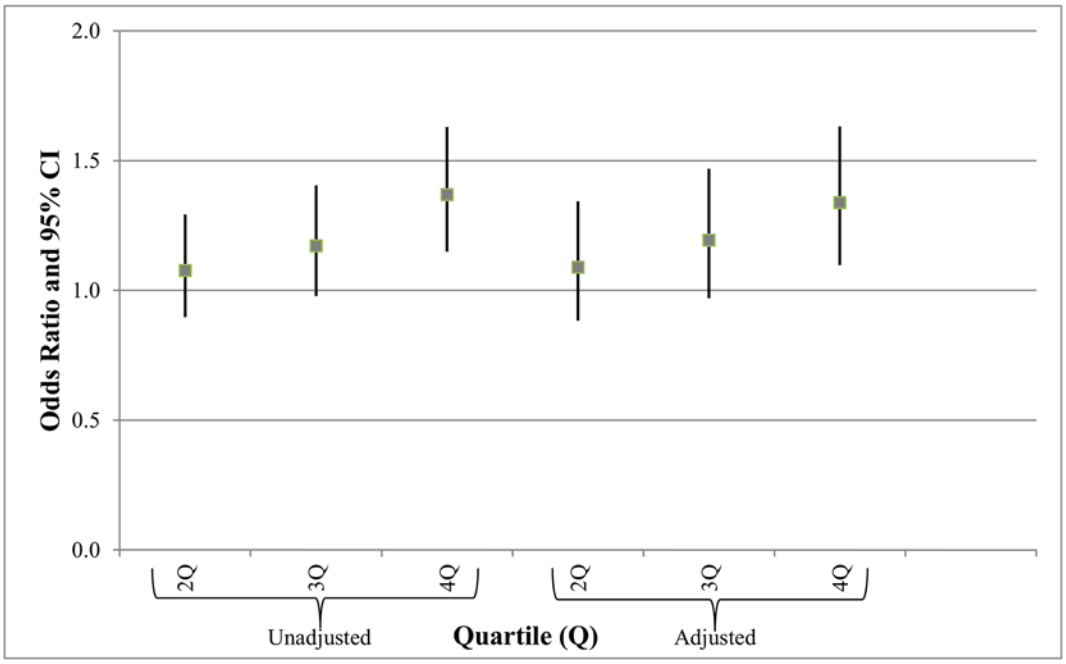

Fig 2. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for small for gestational age (adjusted for mom's age, mom's education, pre-pregnancy weight, gender of infant, prenatal visits, smoking during pregnancy, gestational diabetes, WIC, race, and birth order). Key: Referent (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.

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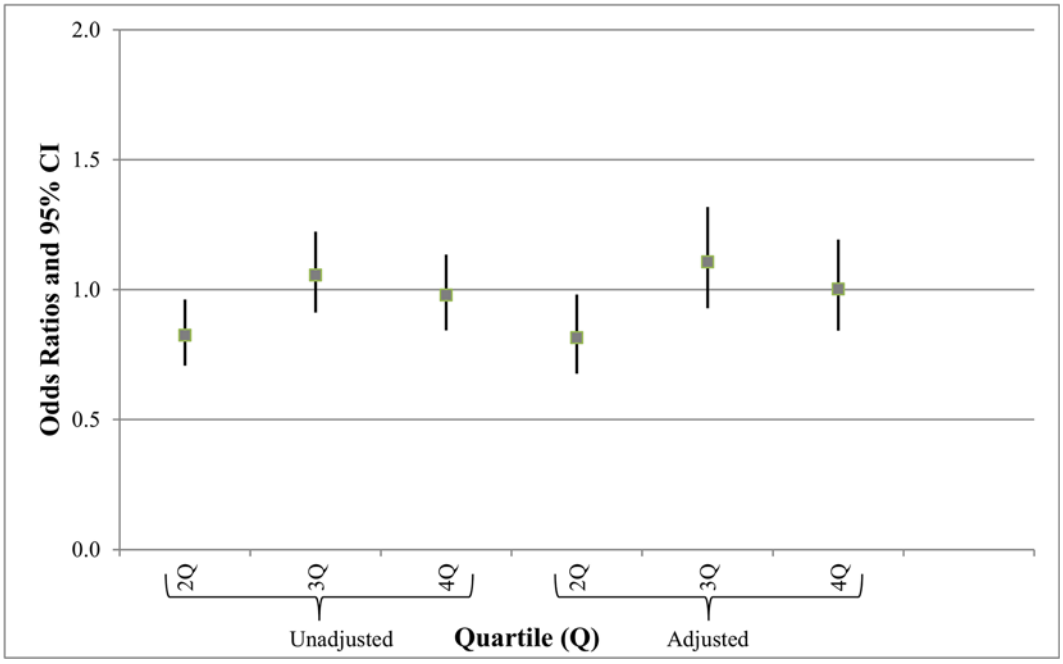

Fig 3. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for prematurity (adjusted for mom's age, mom's education, pre-pregnancy weight, gender of infant, prenatal visits, smoking during pregnancy, gestational diabetes, WIC, race, and birth order). Key: Referent (First quartile), <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.

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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%

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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.

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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.

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

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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.

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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

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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 *i*th 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.

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