ATTACHMENT C

STUDY 1

RESEARCH ARTICLE

Exposure assessment of adults living near unconventional oil and natural gas development and reported health symptoms in southwest Pennsylvania, USA

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Abstract

Recent research has shown relationships between health outcomes and residence proximity to unconventional oil and natural gas development (UOGD). The challenge of connecting health outcomes to environmental stressors requires ongoing research with new methodological approaches. We investigated UOGD density and well emissions and their association with symptom reporting by residents of southwest Pennsylvania. A retrospective analysis was conducted on 104 unique, de-identified health assessments completed from 2012–2017 by residents living in proximity to UOGD. A novel approach to comparing estimates of exposure was taken. Generalized linear modeling was used to ascertain the relationship between symptom counts and estimated UOGD exposure, while Threshold Indicator Taxa Analysis (TITAN) was used to identify associations between individual symptoms and estimated UOGD exposure. We used three estimates of exposure: cumulative well density (CWD), inverse distance weighting (IDW) of wells, and annual emission concentrations (AEC) from wells within 5 km of respondents' homes. Taking well emissions reported to the Pennsylvania Department of Environmental Protection, an air dispersion and screening model was used to estimate an emissions concentration at residences. When controlling for age, sex, and smoker status, each exposure estimate predicted total number of reported symptoms (CWD, $p<0.001$; IDW, $p<0.001$; AEC, $p<0.05$). Akaike information criterion values revealed that CWD was the better predictor of adverse health symptoms in our sample. Two groups of symptoms (i.e., eyes, ears, nose, throat; neurological and muscular) constituted 50% of reported symptoms across exposures, suggesting these groupings of symptoms may be more likely reported by respondents when UOGD intensity increases. Our results do not confirm that UOGD was the direct cause of the reported symptoms but raise concern about the growing number of wells around residential areas. Our approach presents a novel method of quantifying exposures and relating them to reported health symptoms.

Facility Type. We additionally filtered by year, county, and and pollutant as described in our methods. Data can then be exported to a .csv file: http://www.depgreenport.state.pa.us/powerbiproxy/powerbi/Public/DEP/AQ/PBI/Air_Emissions_Report Climate data was retrieved from NOAA's local climatological database. To use the tool, you need to select the state and county of where the airport is located. We used data from the Pittsburgh Allegheny County Airport in Allegheny County, PA. Once the airport has been added to your cart, you can determine the data range you wish to download and request a .csv of the data: https://www.ncdc.noaa.gov/cdo-web/datatools/lcd Health data cannot be shared publicly because some of the data we collect is in rural areas with sparse population. In areas of sparse population, it may be possible to identify participants using data such as GIS coding. Data are available from the Environmental Health Project Institutional Data Access / Ethics Committee (contact via Environmental Health Project, Sarah Rankin 724.260.5504) for researchers who meet the criteria for access to confidential data.

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Introduction

Unconventional oil and natural gas development (UOGD) may represent a health risk due to exposure to chemicals used during the hydraulic fracturing process, on-site emissions, and/or a lack of strict regulations [1–4]. The UOGD process involves a combination of horizontal drilling across shale formations and the use of a heterogeneous fracturing fluid injected into wells at high pressure to fracture shale and release trapped oil and gas. Evidence suggesting associations between UOGD activity and adverse health effects has emerged from multiple studies. UOGD activity has been associated with adverse birth outcomes [5–7], increased rates of hospital use [8–10], asthma [11,12], and upper respiratory and neurologic symptoms [13–15]. These studies have used a variety of approaches to estimate exposure to UOGD, including inverse distance weighting (IDW), cumulative well count, cumulative well density (CWD), well activity metrics, spatiotemporal models, and direct water sampling [6–8,13,16,17].

Given the associations between UOGD development and adverse health outcomes, but lack of resolution on questions pertaining to safe proximity of residency to wells, we sought to determine which variables related to UOGD are associated with a higher number of reported symptoms. For this study, two proximity metrics and one exposure variable constitute our exposure estimates and are referred to as exposure measures throughout this paper. This study was conducted to address the following questions: 1) Which exposure measure(s) best predicts the of number of symptoms reported? and 2) Which individual symptoms are associated with increasing exposure as estimated by each exposure measure? Unlike prior studies, this analysis compares three estimates of exposure: CWD, an IDW measure, and annual emission concentrations (AEC) derived from estimated well emissions within 5 km of a residence. CWD is defined as the count of wells divided by a spatial scale in km^2 [8], while IDW, a similar measure, weights wells according to distance from a residence [6,7]. The AEC measure used publicly available data on wells to estimate concentrations of emission pollution at a residence. Bamber at al. [18] notes that exposure to UOGD is poorly characterized, and this analysis–comparing three estimates of exposure–attempts to address this concern. Though frequently used proximity and density metrics are included in this analysis, the methodological approach taken here has not been used to model emission concentrations at the home nor to predict symptom outcomes associated with increasing levels of exposure. The use of two methodologies applied here (i.e., statistical modeling to analyze the influence of different exposures on symptom reporting, and a technique to identify specific symptoms that might be indicative of exposure) suggests new techniques for studying relationships between health and exposure.

Materials and methods

Study sites & health outcomes

The Southwest Pennsylvania Environmental Health Project (hereafter referred to as EHP) is a nonprofit public health organization in Washington County, Pennsylvania (PA). Between February 1, 2012 and December 31, 2017, 135 children and adults completed health assessments at EHP. Individuals self-selected and approached EHP because of their concerns about exposure to UOGD. Health data were abstracted as described in Weinberger et al. [19] and the same data were used in this analysis.

As described by Weinberger et al. [19] the 135 de-identified health assessments were reviewed retrospectively by a team of health-care providers, including a board-certified occupational-health physician and at least one nurse practitioner. Records were excluded if the respondent was under 18 years old, worked in the oil-and-gas industry, lived outside of PA, or did not fully complete the assessment form (17 excluded). The remaining 118 health assessments were reviewed. Each symptom recorded in the assessment was reviewed and those symptoms that could be plausibly explained by co-occurring medical conditions, medical history, or work and/or social history were excluded. For this analysis, symptoms that remained were grouped into nine categories: general; lung and heart; skin; eyes, ears, nose, and throat (EENT); gastrointestinal (GI); nerves and muscle; reproductive; blood system; and psychological. For this analysis, we restricted the sample to residents of southwest PA with known latitude and longitude data for their residence (14 individuals excluded). The study population included individuals from eight counties: Washington, Greene, Beaver, Butler, Allegheny, Bedford, Fayette, and Westmoreland (Fig 1). This resulted in a convenience sample of 104 adults. This study was approved by the New England Institutional Review Board and the Chatham University Institutional Review Board.

Exposure measures

Cumulative well density and inverse distance weighting. Home address was collected at the time of the health assessment. For this analysis, the address was used to determine the latitude and longitude coordinate of the residence of each respondent [21].

The PA Department of Environmental Protection (PA DEP) publishes active well locations and reported emissions on an open-access online portal [22]. The emissions inventory provides well location data in latitude and longitude coordinates and emissions data by pollutant

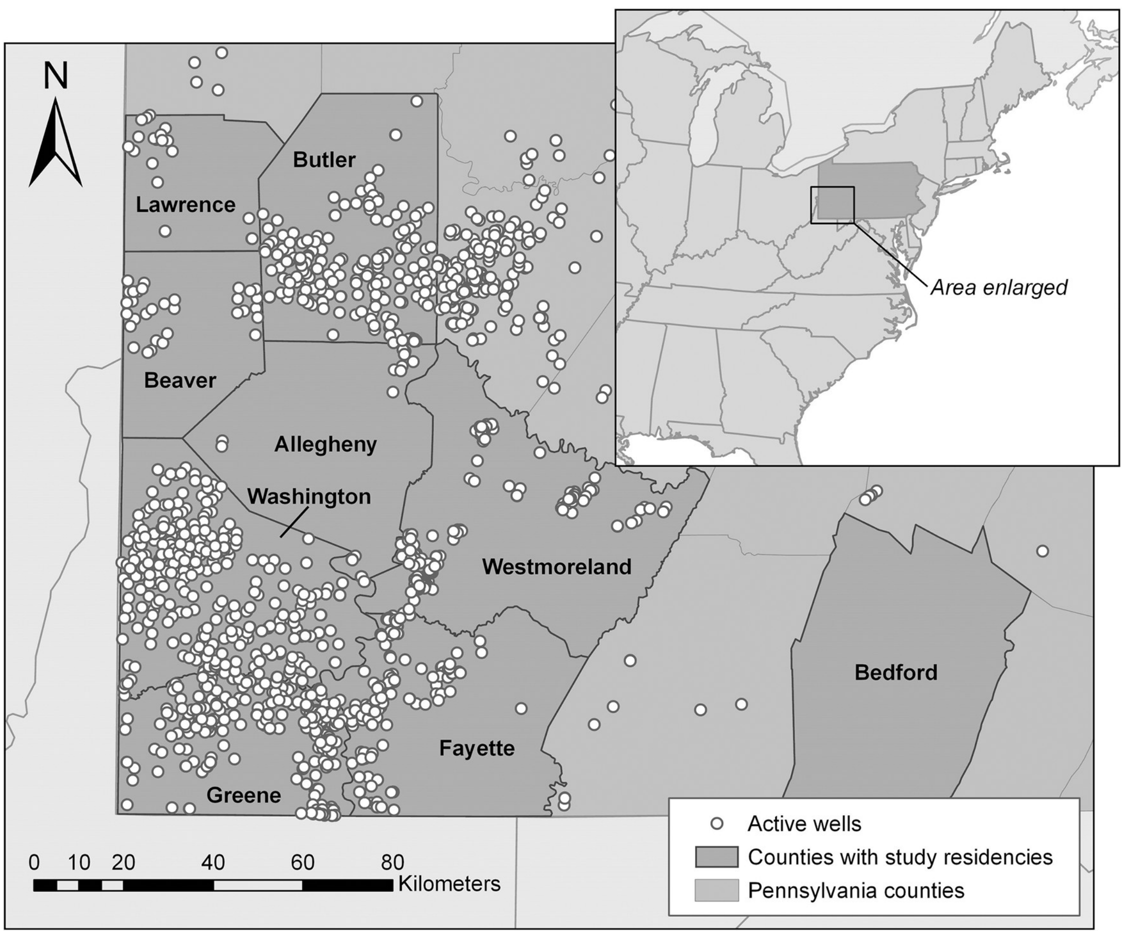

Fig 1. Study area and active well locations. Southwestern PA study location and active wells in 2016. No respondents lived in Lawrence County; however, a respondent in Butler County lived near the county border. Map was made with ArcGIS Desktop [20].

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type for each well. For assessments completed between February 1, 2012 and December 31, 2017, ArcGIS ArcMap 10.3 [20] was used to plot the latitude and longitude of each respondent's residence alongside all active, unconventional wells within a 5-km radius around the residence during that year. A CWD was calculated for each respondent by dividing the number of wells in a 5-km radius around the home by the area of the radius.

An IDW calculation was also applied as a second method for quantifying exposure intensity. This measure applies more weight to wells located closer to a residence than to those located farther away. The inverse distance of each well within a 5-km radius of a residence was calculated, and those values were summed into one IDW score per residence as shown in the following equation:

$$IDW\ density = \sum_{i=1}^{n} {}^{1}/_{d_i} \tag{1}$$

where distance (*d*) is kilometers between the well (*i*) and respondent's residence, and *n* is the number of wells within the 5-km radius [5,13]. For this analysis, only wells located within PA state lines were included in the calculations due to a lack of data availability from neighboring states. Four residences' 5-km radius crossed into neighboring West Virginia. For these sites, the radius percentages outside of Pennsylvania were 0.6%, 4.4%, 10.7%, and 14.3%.

Annual emissions concentration. Annual emissions inventories for 2012 through 2017 were exported from the PA DEP's database. Sources reported on the emissions inventory included venting and blowdown, dehydration units, drill rigs, stationary engines, pneumatic pumps, fugitive emissions, and emissions produced during the well completion stage. Sources of emissions that are not represented in the inventory include flaring, off-gassing from contaminated water, and truck traffic. A review of the PA DEP's emissions-inventory data revealed six compounds had the highest reported volume expressed in tons/year: carbon monoxide, nitrogen oxides, particulate matter ($PM_{2.5}$), aggregated volatile organic compounds (VOCs), methane, and carbon dioxide [22]. To estimate emissions at the residence, we used carbon monoxide, nitrogen oxides, $PM_{2.5}$, and VOCs because they had known health effects at the expected level of exposure; methane and carbon dioxide did not so were not included despite being two of the top six compounds emitted. For this study, tons/year was converted to grams/hour.

A complete explanation of how concentrations at a residence were estimated can be found in Brown et al. [23] and will briefly be described here. To estimate emissions concentration at a respondent's residence, an atmospheric dispersion box model was used to determine air dilution downwind from emission sources (wells) and estimate the concentration of compounds at a residence. The model assumes a theoretical box, or volume, of air carries emissions downwind from a well. As the box moves away from the source, the size of the box increases, and the concentration of pollutants is proportionally diluted. The initial concentration is inversely proportional to the rate of speed with which the box moves over the source. The vertical and lateral expansion of the box as it moves downwind is determined by weather and wind speed. This screening model estimates the level of air dilution during dispersion using three parameters: 1) cloud cover, 2) wind speed, and 3) time of day. These parameters are taken from Pasquill [24]. His report identifies six stability classes and five wind speeds that characterize the meteorological conditions that define these classes [25,26]. Using these conditions, we applied hourly cloud cover and wind speed data retrieved from the National Oceanic and Atmospheric Administration (NOAA) for the years 2012 through 2017. To ensure a complete set of weather data for each year of the study, we chose to use data from one major airport in southwest PA, the Pittsburgh Allegheny County Airport in West Mifflin, PA, in the model [27]. We were able to establish hourly conditions over a year and apply the estimates to each residence in our sample, to determine an annual level of exposure for each residence. Estimates of annual average exposures were based on weather patterns for each year over the entire region.

After our screening model was established, we used the weather data to calculate hourly concentrations from a reference well, estimated to emit 300 grams of a compound per hour, to standardize the formula when calculating how other wells deviate from a given reference [23]. Once hourly concentrations were computed for the reference case, we calculated a 90th percentile emissions concentration value (μg/m^3) for distances of 0.5 km, 1 km, 2 km, 3 km, and 5 km in the four directional quadrants around the reference well. The resulting values represent varying exposure levels experienced at a given residence living between 0.5–5 km from the reference well. The hourly emissions are assumed proportional to the 300 grams/hour reference. Using the PA DEP data for the year corresponding to the respondent's health assessment, the emissions of carbon monoxide, nitrogen oxides, $PM_{2.5}$, and VOCs in grams/hour were summed into one total for each well.

Well sites are ubiquitous around residences in these counties, so we used the model to first calculate a residence's exposure for the four directional quadrants. Within a quadrant, the distance of each well from the residence was determined and, depending on the distance, the 90th percentile concentration value was assigned to that well. Then, the total emissions from the well, in grams/hour, was multiplied by the 90th percentile concentration value and divided by 300 grams/hour to derive the deviance from the reference in each quadrant. The outputs give μg/m^3 per well for each directional quadrant in a 5-km radius. The estimated emission concentrations from each well, across all quadrants, were added together into an annual total exposure value per residence. The total exposure value was used as the AEC measure in the analysis.

Statistical analysis

All statistical analyses were executed in the R Project for Statistical Computing [28]. Model comparisons were made using glmutli version 1.0.7.1 [29], and TITAN analyses with TITAN2 version 2.1 [30].

The analysis consisted of two approaches to address the research questions: generalized linear models (GLMs) to test the association between the number of symptoms reported and the intensity of each exposure, and Threshold Indicator Taxa Analysis (TITAN) to predict which specific symptoms were most likely to be reported with increasing intensity of each exposure measure. Each individual symptom reported in the health assessment was binomially coded per respondent with 1/0 for yes/no. An alpha level of $< = 0.05$ was used as a threshold for significance in both tests.

Because the dependent variable followed a Poisson distribution, GLMs were used for modeling. For each exposure GLM, a tool was used to automate statistical model selection by generating all possible unique combinations of our demographic variables with each exposure measure to identify the best-fit statistical model for each exposure measure against total number of symptoms. Our demographic variables included: age, sex, smoking status, and water source. All demographic variables were included in the selection tool and, by default, 100 potential models were generated *a priori* to determine the best fitting models. To choose our model, Akaike information criterion (AIC) values, with a correction for small sample sizes, and number of terms for each output model were compared [31]. Lower AIC values are associated with simpler models that exclude irrelevant terms, so when comparing models, the model with the lowest AIC is considered optimal [32,33]. The best model is the one with the lowest or second-lowest AIC score and then statistically assessed for each exposure variable [34]. Interactions between variables were excluded from the best model to increase model parsimony and only explore main effects. Zero-inflation was not required for our data as only 15% of the sample reported no symptoms. To determine our radius distance around the home, we applied GLM analyses using three spatial scales of cumulative well density: 1, 2, and 5 km. AIC criterion was used to determine which scale to study.

To assess how individual symptoms were related to changing density (CWD and IDW) and AEC, we applied the TITAN methodology. TITAN is a non-parametric analysis traditionally applied in the ecological sciences, but increasingly applied in environmental science [35], where the presence/absence of a species (also referred to as taxon) among different samples of communities is used to assess nonlinear community-scale responses, both positive and inverse, to changes in their environment. Environmental gradients are used in this process to express how an exposure is increasing in the studied environment. The primary goal in TITAN is to determine if there are levels of exposure along the gradient that influence a statistically significant positive or inverse response and are associated with the presence or absence of one or more specific species. The relationship of each species is assessed via an indicator value that ranges from 0 to 100, with 100 representing a perfect indication of species-specific association with the gradient. The TITAN analysis allows for the consideration of species that have low occurrence frequencies to identify those that possess high sensitivity to the environmental gradient. For example, Khamis et al. used the TITAN methodology to determine how reductions in glacier melting influence the presence and absence of certain aquatic species in rivers and lakes [36–38].

For this study, we defined communities as individual respondents and species as the specific symptoms reported to identify the degree to which each symptom represented a statistically significant indicator of UOGD exposure (CWD, IDW, and AEC). To remove symptoms with frequencies too low to detect a pattern, we only included symptoms reported five or more times into the TITAN analysis (n = 50) [39]. Indicator values were considered statistically significant at an α of 0.05, and resulting symptoms were organized by those having a frequency greater than 10 and a z-score greater than or equal to 1. To our knowledge, this is the first use of TITAN methodology in public health research (S1 Appendix).

Results

Symptom reporting characteristics

In this convenience sample of 104 adults who presented health concerns about UOGD, 59% were female with a median age of 57. In this predominantly rural area, only a third reported using municipal water for household use with the majority relying on private wells, cisterns, or springs. Smoking status was available for 78 of the 104; of those, 40% reported either current or former smoking. The number of individual symptoms reported by individuals ranged from 0 symptoms to 36, with mean of 7 symptoms and a standard deviation of ± 7.7 symptoms per person. Table 1 shows the most frequently reported symptoms.

Generalized linear models: Symptom total

Initial GLMs to test the three spatial scales against symptom total showed that models using 5 km as the radius had the lowest AIC value and were therefore selected in our study (1 km: AIC = 1095.26, 2 km: AIC = 1039.73, 5 km: AIC = 1027.65). Between the three exposure measures, Pearson correlation coefficients ranged from 0.03 to 0.60; thus, all three were tested independently against total reported symptoms. Final GLMs for each exposure measure included sex and smoker status as statistically significant individual predictors, while age was not found to be statistically significant. Sex and smoker status were modeled as categorical

Table 1. Ten most frequently reported symptoms by number and percent of respondents (n = 104).

Symptom	*n*	*n (%)*
Sore Throat	34	33
Headache	34	33
Difficulty Speaking	34	33
Cough	32	31
Itchy or Burning Eyes	30	29
Stress	30	29
Shortness of Breath/Difficulty Breathing	26	25
Anxiety/Worry	26	25
Fatigue	21	20
Sinus Infection	20	19

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variables, while age was treated as continuous. Water source was excluded during the model selection process and was not included in the final models.

When controlling for age, sex, and smoker status the exposure measures produced the following results: CWD, IDW, and AEC predicted total reported symptoms ($p<0.001$, $p<0.001$, $p<0.05$ respectively). Based on comparisons of AIC values, CWD (AIC = 780.91) appeared to be more closely related to adverse health symptom reporting compared to IDW (AIC = 803.13) and AEC (AIC = 831.95; Table 2; Fig 2).

Table 2. GLM model results for each exposure variable against total reported symptoms.

Model	Variable	Estimate	Std. Error	Z statistic	P value
CWD					
	Intercept	1.339	0.257	5.220	<0.001
	Ever Smoked	0.520	0.088	5.921	<0.001
	Sex	0.486	0.094	5.156	<0.001
	CWD	0.840	0.102	8.267	<0.001
	Age	-0.002	0.004	-0.605	0.545
	Residual degrees of freedom	73			
	AIC	780.91			
IDW Score					
	Intercept	1.407	0.253	5.563	<0.001
	Ever Smoked	0.492	0.088	5.615	<0.001
	Sex	0.487	0.094	5.184	<0.001
	IDW Score	0.015	0.002	6.245	<0.001
	Age	-0.002	0.004	-0.461	0.645
	Residual degrees of freedom	73			
	AIC	803.13			
AEC					
	Intercept	1.508	0.250	6.029	<0.001
	Ever Smoked	0.544	0.087	6.252	<0.001
	Sex	0.550	0.094	5.855	<0.001
	AEC	5.74×10^{-6}	2.35×10^{-6}	2.444	<0.05
	Age	-0.003	0.004	-0.758	0.449
	Residual degrees of freedom	73			
	AIC	831.95			

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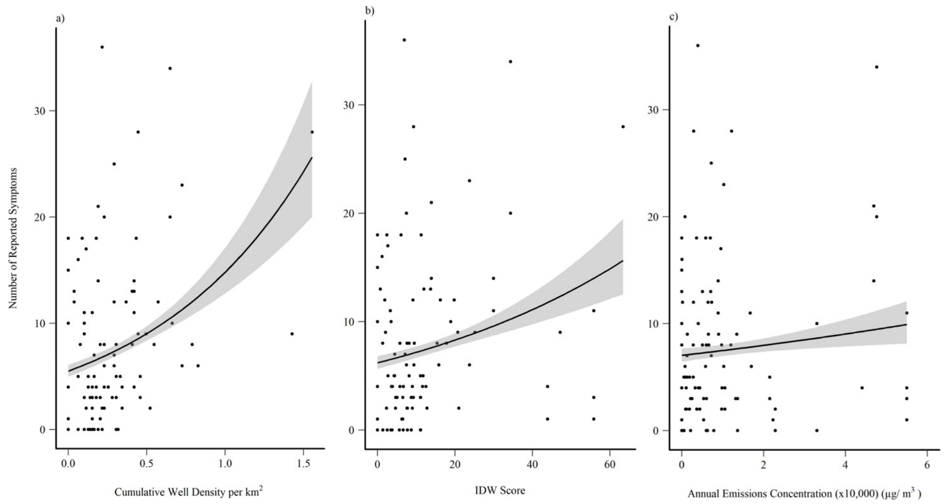

Fig 2. Exposure model plots. Poisson distributed generalized linear model for total symptoms and a) CWD, b) IDW score, and c) AEC as the exposure measure. A 95% confidence interval was applied around the regression line.

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TITAN analysis

The TITAN analysis identified multiple statistically significant symptoms along gradients of CWD, IDW, and AEC ($\alpha< = 0.05$). The higher the indicator value, the more likely the symptom is to be seen with an increase in exposure. Twenty-wo symptoms were associated with the gradient of CWD (Fig 3) with itchy or burning eyes as the strongest, positive indicator value along the gradient (indicator value = 59.31), followed by stress (indicator value = 47.17) and dry skin (indicator value = 44.44). Headache, difficulty sleeping, sore throat, stress, and itchy or burning eyes were the five most frequent symptoms in this gradient. Of the twenty-two statistically significant symptoms, approximately, 27% were categorized as EENT symptoms, followed by nerve and muscle symptoms at 27% as well. Four symptoms were inversely associated with the gradient. Although this is counterintuitive, given that 50 symptoms were

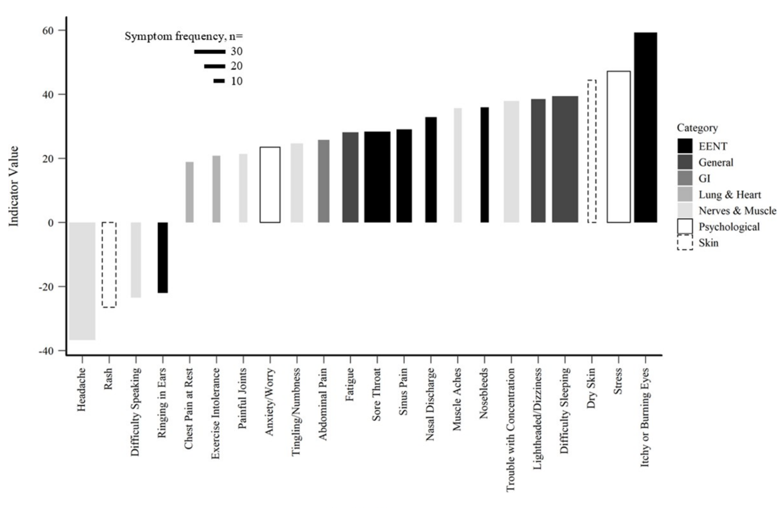

Fig 3. CWD TITAN results. Individual symptoms by indicator value along the gradient of CWD. Indicator values range 0–100, with 100 being a perfect association with the gradient. Bar width represents symptom frequency.

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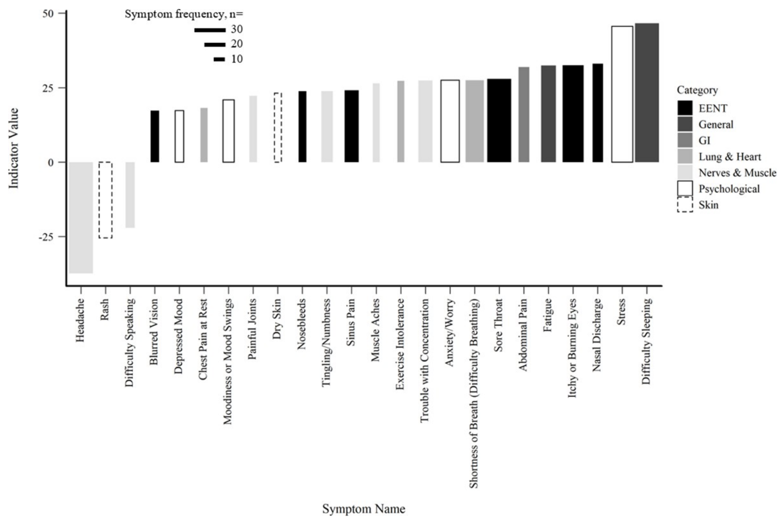

Fig 4. IDW TITAN results. Individual symptoms by indicator value along the gradient of IDW. Indicator values range 0–100, with 100 being a perfect association with the gradient. Bar width represents symptom frequency.

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assessed along each gradient, one would expect a small number of symptoms be statistically significantly associated with gradients as type-I errors.

Twenty-four symptoms were statistically significantly associated with the gradient of IDW (Fig 4), with difficulty sleeping as the strongest, positive indicator (indicator value = 46.6), followed by stress (indicator value = 45.58), and headache (indicator value = 37.7), though this particular symptom was inversely associated with the gradient. In addition to headache, difficulty speaking, and rash were also inversely associated with the gradient. The top five most frequent symptoms were the same as those in the gradient of CWD. Of the twenty-four statistically significant symptoms, approximately 25% were EENT; 25% were nerves and muscle symptoms; 17% were psychological symptoms.

Seventeen symptoms were statistically significantly associated with the gradient of AEC (Fig 5). Difficulty sleeping represented the strongest, positive indicator value (indicator

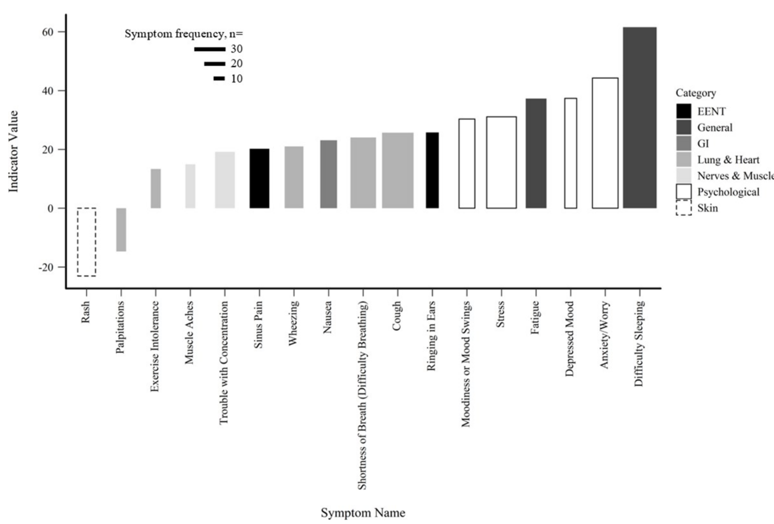

Fig 5. AEC TITAN results. Individual symptoms by indicator value along gradient of AEC. Indicator values range 0–100, with 100 being a perfect association with the gradient. Bar width represents symptom frequency.

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value = 61.58), followed by anxiety/worry (indicator value = 44.29), and depressed mood (indicator value = 37.36) which were both positively associated. Two symptoms were significantly inversely associated with the gradient of AEC. The top five most frequent symptoms of this gradient were: difficulty sleeping, anxiety/worry, cough, stress, and shortness of breath (difficulty breathing). Of the seventeen significant symptoms, roughly 29% were lung and heart symptoms; 29% were psychological.

Discussion

Despite a high degree of inherent complexity in associations between health and UOGD, a growing body of evidence, including our findings, suggests that the impacts of UOGD are heterogeneous and consistently detectable even at distances considered safe by some regulations. Determining the best method for quantifying UOGD intensity from a health standpoint is still unknown; however, we detected links between each exposure measure and total symptoms reported, including effects detected at a farther range (5 km) than reported in other studies [15,19]. Variation in UOGD operations can include the size, operation duration, and heterogeneity in chemicals used which adds complexity when attempting to relate operations to health symptoms. Discerning other influences on health that are not UOGD related or interact with UOGD in ways that have not yet been studied is an additional challenge. Other environmental stressors compounded with UOGD, or the inclusion of other UOGD infrastructure like pipelines and compressor stations, further such complexity. The use of amended IDW metrics, such as employed in Koehler et al. [40], attempts to expand IDW by including well development phases to better define exposure. Regardless, the consensus of studies reporting on health impacts around UOGD infrastructure suggests consistency between variables. The aggregate of these analyses suggests that regardless of how exposure to UOGD intensity is quantified, the impacts may occur at broad spatial scales and using distance to just the nearest UOGD facility may underrepresent risks to health.

The method of estimating UOGD intensity appears to affect the strength of associations between exposure and health outcomes in our study, but overall, a positive relationship was found between CWD, IDW, and AEC and total reported health symptoms within a 5-km radius of respondent homes. Brown et al. [23] did not find an association with the median AEC. This apparent inconsistency may be explained by their use of the median AEC, rather than the 90th percentile AEC used in this study.

Our model accounts for variation in the results that may be linked to our demographic variables. By doing so, our model terms related to exposure can account for the weight of UOGD after the variability of our demographic variables has been factored out. Relative to AEC and IDW measures, our findings indicate that CWD in proximity to residences, which constitutes a more simplistic measure, was more closely linked to total symptom reporting (Fig 2A). Exposure measures like CWD and IDW are considered proximity metrics and do not define an exact exposure pathway from source to residence; however, we hypothesize that adverse health symptoms could occur through inhalation of chemicals in UOGD emissions and that an increase in the density of wells would, together, create an exposure route. Given that both proximity and a better-defined exposure measure of AEC were significant, future studies should explore links between these measures on their own.

Our challenge to predict adverse health symptoms may reflect the general challenge of condensing well operations into a single, simple metric due to variation in each operation. Studies often apply only one metric for exposure, which could potentially overlook effects that may be seen if the measure were more precise and if more detailed UOGD data were readily available. Regardless of our findings, additional inquiries that compare health outcomes associated with exposure magnitude coupled with real-time live air monitoring are needed to determine which measure best quantifies exposure.

Our results also caution against limiting investigations of UOGD impacts on health within symptom categories due to the mixed suite of effects reported by respondents. For example, our model assessing the relationship between total symptoms and IDW, and total symptoms with AEC, suggested relatively limited predictability (Fig 2B & 2C). However, the respective TITAN analyses included nearly as many significant symptom associations compared to the CWD model (24 and 17 statistically significant indicators, respectively). Other studies have limited analyses to symptom categories, which may lead to underreporting of impacts to health across the literature, as individual symptoms have been classified under different categories [13,15,41]. A closer look at category composition in other studies revealed that itchy or burning eyes, sinus pain, fatigue, stress, and anxiety/worry are specific symptoms reported by individuals, consistent with our findings in the TITANs [14,15,42,43]. Psychological symptoms, such as stress and anxiety/worry, were included in the top five symptoms either together or separately in each of our models, with the highest percentage of psychological symptoms found in the gradient of AEC. Studies have found that increased air pollution can be linked to psychological distress, while others have found that increased stress, depression, and anxiety can be experienced by people living in communities with UOGD [14,15,42–44]. Furthermore, Albrecht [45] notes that environmental change can cause human distress, which is supported by Lai [46] who found that negative perceptions of UOGD were associated with negative psychological states. The individual symptom counts increased along exposure gradients (Figs 3–5), suggesting subtler effects when compared to aggregate symptom total (Fig 2).

Our results also caution against emphasizing a single symptom to represent detrimental health in association with UOGD. Given the suite of various chemicals applied in UOGD operations and statistically significant interactions between UOGD exposures and demographic variables as highlighted by our GLM models, substantial weight of evidence is needed to conclude that a single symptom is likely to increase with UOGD intensity. The TITAN analyses identified four, three, and two symptoms that were statistically inversely related to the gradients of CWD, IDW, and AEC. Regardless of these anomalies, 18 out of 22, 21 out of 24, and 15 out of 17 statistically significant indictor symptoms were positively associated with the gradients of CWD, IDW, and AEC which contributes further evidence that UOGD impacts health in a heterogeneous manner.

Limitations & recommendations

As with any work attempting to relate the severity of health impacts to an environmental stressor, our study findings must be considered in the context of the study limitations. Our convenience sample consisted of individuals who presented to EHP because they had concerns about health effects associated with exposure to UOGD, limiting generalizability. Additionally, the health records lacked detailed information about symptoms onset, duration, and severity, or the nature of the symptom (i.e., episodic or chronic). Our lack of detailed information in our symptom data is a limitation of this study. The health records are also subject to recall bias, with the potential for over-reporting of symptoms particularly since respondents presented due to concern about health impacts of UOGD. One mitigating factor is that at the time of reporting their symptoms the respondents did not know their records would be reviewed for this study, nor did they know the exposure measures that would be used. Future studies should collect detailed symptom data and exposure measures in real-time to address these issues.

A further limitation of our study concerns available exposure data. Not all sources of emissions are included in data released by regulatory agencies, and activities such as flaring, off-gassing from contaminated water, and truck traffic may contribute to total emission rates, but are not currently reported [47–49]. In addition, we were limited by available emissions data, which is reported on an annual basis. Some studies suggest that of the development and production stages, the hydraulic fracturing phase of development and the flowback phase of production account for the highest levels of emissions [3,40,50] and future work should include developing exposure measures that capture and isolate these stages.

The air-and-exposure screening model may have also underestimated actual emission concentrations because the model assumes emissions are constant over a year for all sources and does not factor in varying levels of emissions associated with well development phase. Furthermore, our model treats the trajectory of each well's emissions plume equally when summed into one AEC value. Future work should factor wind direction into the model to estimate and correct for the influence wind direction plays on plume movement and concentration to improve upon the AEC value. Additionally, the box model does not correct for influences of topography [25], so we could not compare emission concentrations of various elevations. Regarding weather data, one limitation was that weather data was only taken from one airport for our sample.

Conclusion

This study was unique in its attempt to use an analytical tool taken from ecological research to determine specific symptom sensitivity to changes in CWD, IDW, and AEC from UOGD. The consistency in relationships between UOGD operations, regardless of how UOGD is quantified, and adverse health outcomes across the literature suggests that increases in symptoms could be related to higher exposure to emissions or chemicals used on the well pad [3,5,11,50]. The impact of fracking on health requires ongoing research because of continued industry growth, the relatively young age of the field, and the potential for chronic or latent illness, like cancer or developmental health impacts, to result from long-term exposure [1,51]. Our results do not confirm direct causal links between UOGD exposure and reported symptoms, but they do suggest that living in proximity to wells may be associated with health symptoms. Our findings suggest that an estimation of exposure that relies only on proximity may be simplistic, particularly in communities with increasing density of wells at 5-km scales, and that a deeper understanding of emissions composition and potency at the residence level is warranted. Future research should examine the question of how the aggregation of exposure affects health.

Supporting information

S1 Appendix. TITAN example code and explanation. Lines 7–13 prepare a sample dataset of twenty potential symptoms and fifty individual respondents to mimic a subset of the data used in this study. For each respondent, 1s and 0s were used randomly for each symptom. A 1 means they did have that symptom, 0 means they did not. Now we have a dataset of fifty respondents and what symptoms they did or did not have. Line 16 creates a randomized list of exposure, one for each of the fifty respondents. In our study, each respondent had a measure of cumulative well density (CWD), an inverse distance weighting (IDW) score, and a measure of estimated annual emissions concentration (AEC). Line 16 creates an exposure variable that ranges from 0 to 50 (no units), with 0 being no exposure and 50 being representative of high exposure, though in our sample there was no limit to how high an exposure measure could go. Line 19 uses titan() to run the TITAN analysis, taking the reported symptoms and exposure values to determine if certain symptoms occur more or less at different levels of exposure. For

example, when the exposure measure reaches 12, the model is looking for any symptoms that stand out as occurring more frequently at that exposure level. Indicator values (range 0–100) are used to score each symptom's relationship to that exposure level, or gradient. A high indicator value shows a strong relationship with the gradient at a certain level. Then, the model determines if that relationship is positive or inverse. In ecological studies, one might study how changes in dissolved oxygen (DO) in a pond ecosystem cause certain species to die off or thrive as levels of DO change. When we begin to see a certain species appear in the pond, we can hypothesize that there may also be a change in DO as well since that species is an indicator of a certain threshold, or level of DO. Lines 22–29 takes information from the TITAN analysis and creates a table. For this table, the rows each represent the different symptoms, while columns are information pertaining to Indicator Value, the frequency of the symptom, p-values, whether the symptom is positively or inversely associated with the gradient, and the z-score. Using these parameters, we begin to filter out symptoms that were infrequent (line 25) and can also filter out insignificant symptoms or symptoms with low z-scores (lines 40–41). The latter two were done in our study but did not make sense for this sample data. Lines 34–36 construct the final plot we used to visualize the results of the TITAN analysis. In the plot, there are ten symptoms positively associated with the gradient with indicator values ranging from 32 to 71. The same goes for the inversely associated symptoms. For the plots in our study, we added additional characteristics like colors to group symptoms into categories and using the width of each bar to represent the frequency of symptoms being reported.
(R)

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ATTACHMENT C

STUDY 2

Final Report

for

Pennsylvania Department of Health,
Bureau of Epidemiology

Hydraulic Fracturing Epidemiology Research Studies: Birth Outcomes

Prepared by:
University of Pittsburgh
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Birth Outcomes Cohort Study

Background

Over the last 25 years, the American energy landscape has undergone an evolution, perhaps most notably with the expansion of hydraulic fracturing operations[1]. From 2000 to 2015, the number of hydraulically fractured wells in the United States increased from 23,000 to approximately 300,000. This rapid growth has corresponded to a range of economic benefits, including decreased energy costs and greatly increased production of both oil and natural gas[2]. However, mounting evidence suggests that hydraulic fracturing may have adverse impacts on public health and the environment[3-24].

Hydraulic fracturing – also known as fracking – is a process of unconventional natural gas development (UNGD) done by injecting large amounts of fluid at high pressure into dense rock in order to free trapped oil and natural gas[25]. The fluid used for injection typically consists of a mixture of water, sand (or other proppants), and various chemical additives. These wells, which are typically deeper than conventional wells, access previously unavailable reservoirs of oil and natural gas trapped in shale. The Marcellus Shale formation encompasses approximately half of Pennsylvania and is a large reservoir of natural gas.

Studies examining the associations between UNGD and birth outcomes, including small for gestational age (SGA), preterm birth, and lower term birthweight, have found inconsistent results. Table 1 summarizes results from studies examining associations between birth outcomes and exposure to UNGD (additional details can be found in Appendix Table 1). Five of the fourteen studies included in Table 1 were conducted using births in Pennsylvania (PA), which was the most commonly represented state. Other states included were California (n=2), Colorado (n=2), Oklahoma (n=1) and Texas (n=4).

Six studies examined associations with SGA[5,6,10,18,26,27]. Of these, three found associations and three did not. Among those that found associations, estimates of increased risk ranged from 18%[26] to 34%[5]. Two of the three studies conducted in PA bracketed the range of associations (Hill[26], with an increase of 18% over the mean rate, and Stacy[5], with an odds ratio of 1.34 comparing most to least exposed) and the third found no association (Casey[6]).

Nine of the fourteen studies examined preterm birth[5,6,10,12,17,23,26,28,29]. Of those, five of the nine studies did not find an association[5,17,23,26,29] while the remaining four reported an association[6,10,12]. Increased risk of preterm birth ranged from 14%[10] to 40%[6]. Of the three studies that examined preterm births in PA, two found no association (Stacy[5] and Hill[26]) while Casey[6] found the highest increased risk of any of the studies (40%), associated with the highest tertile of exposure.

Nine studies also investigated the association between birthweight and UNGD[5,6,10,18,22,23,26,27,30]. Of those, six[5,18,22,26,27,30] of the studies found associations, ranging from 19 grams[30] to 50 grams[26] reduced birthweight, while three[6,10,23] did not. Of the four studies examining birthweight conducted in PA, three[5,22,26] found associations, ranging from reductions in birthweight from 21 grams[5] to 50 grams[26], and one did not (Casey et al.[6]).

Table 1. Summation of Literature Examining Associations Between UNGD and Birth Outcomes

Year	First Author	State	SGA	Preterm Birth	Reduced Birthweight	Birth Defects
2014	McKenzie[23]	CO	--	N	N	Y/N[1]
2015	Stacy[5]	PA	Y	N	Y	--
2016	Casey[6]	PA	N	Y	N	--
2016	Ma[7]	PA	--	--	--	N
2017	Currie[22]	PA	--	--	Y	--
2017	Whitworth[10]	TX	N	Y	N	--
2018	Hill[26]	PA	Y	N	Y	--
2018	Whitworth[12]	TX	--	Y	--	--
2019	Janitz[31]	OK	--	--	--	Y/N[2]
2019	McKenzie[24]	CO	--	--	--	Y[3]
2020	Cushing[28]	TX	--	Y	Y	--
2020	Gonzalez[17]	CA	--	N/Y[4]	--	--
2020	Tran[29]	CA	Y[5]	N	Y[5]	--
2021	Willis[18]	TX	N	--	Y	--

1 – Association observed with congenital heart defects and neural tube defects but not oral clefts
2 – Association observed with neural tube defects but not congenital heart defects or oral clefts
3 – Association observed with congenital heart defects
4 – Association only observed in very preterm births (<31 weeks)
5 – Association only observed in rural and not urban areas

The study conducted by Casey et al.[6] in Eastern Pennsylvania had many strengths. They formed their cohort using electronic health record data on 10,946 infants born between January 2009 and January 2013. They estimated cumulative exposure to UNGD activity using an inverse-distance squared model that incorporated distance to maternal residence and information about four phases of well activity: well pad development, drilling, and hydraulic fracturing; and production during pregnancy. However, their time period is relatively short and early in the development of UNGD activity in PA. They also included all wells in the state in their metric as opposed to enforcing any buffer distances from residences to wells. They examined associations between well activity and four birth outcomes: small for gestational age, preterm birth, term birthweight, and low 5-minute Apgar score. As noted in Table 1, Casey et al. found evidence of an association with preterm birth, with an odds ratio of 1.4 (95% CI 1.0-1.9) in the highest quartile of well activity. They did not find any associations with term birthweight, small for gestational age, or low Apgar score.

This retrospective cohort study of birth outcomes had three specific aims: 1) to replicate earlier studies conducted in Eastern PA using a population in Southwestern PA, where UNGD has proliferated in the past 15 years; 2) to enhance and improve upon previous UNGD exposure characterizations by assessing the associations between the most studied birth outcomes and each the four phases of UNGD; and 3) to enhance and improve upon previous UNGD exposure characterizations by assessing whether associations varied by multiple buffer distances to individuals' residences.

Methods

Birth Record Data

Birth data were retrieved from the Bureau of Health Statistics and Research, Department of Health, Pennsylvania for years 2010 to 2020 following Institutional Review Board (IRB) and Protected Access approvals.

Inclusion and Exclusion Criteria

We included live births between January 1, 2010, and December 31, 2020 to mothers residing in the eight-county study area (Allegheny, Armstrong, Beaver, Butler, Fayette, Greene, Washington, and Westmoreland counties).

Exclusion criteria for the study were: Serious birth defects identified at birth; Multiple (non-singleton) birth; Unknown gestational age; Gestational age <22 weeks (pre-viability); Gestational age >41 weeks (post-term); Birth weight <500 g; and Maternal residence located outside the eight-county study area or within the City of Pittsburgh (see Appendix Table 2).

Outcome Measures

Of *a priori* interest were four birth outcomes:

1. **Low 5-minute Apgar score -** A standardized method for assessing the status of a newborn 5 minutes after birth based on five criteria, including heart rate, respiratory effort, reflex irritability, muscle tone, and color [32,33]. Each criterion is given a score of 0, 1, or 2. These scores are summed for an overall score, ranging from 0-10. A low 5-minute Apgar score was defined as a score less than 7.
2. **Small for gestational age -** Neonates with birthweights less than the 10^{th} percentile for their gestational age[34]. Small for gestational age was defined as less than the sex-specific 10^{th} percentile of weight for each week of gestation using United States birth weight reference data from Talge et al. [35].
3. **Preterm birth -** Births occurring between 22- and 36-weeks gestation. Moderate-to-late preterm births were defined as those occurring between 32-36 weeks gestation.
4. **Term birthweight -** Birthweight in grams for birth occurring between 37- and 41-weeks gestation.

Covariate Definitions

Each birth was assigned to a community based on the latitude and longitude of the birth residence associated with the record. Mothers with multiple births could have been assigned to different communities if they changed addresses between births. Community was defined as townships, boroughs, municipalities, or tracts within cities (i.e., Minor Civil Division (MCD) or component Census tract of city MCDs; Schwartz et al., 2011).

Clinical and demographic features of the neonate and mother were included as covariates to control for potential confounding, as shown in Table 2.

Table 2. Clinical and demographic covariates from birth records

Covariate	Definition
Neonate sex	Neonate sex (male, female, unknown)
Gestational age (weeks)	Obstetric estimate of gestation from the birth certificate
Maternal age (years)	Mother's age at delivery
Maternal single race (self-designated)	White Black or African American All other races Unknown or refused
Maternal Education	Less than High School: 8th grade or less, 9th-12th grade but no diploma High School or GED: High School graduate or GED completed Some college: Some college credit but not a degree, Associate's degree Bachelor's or Graduate degree: Bachelor's degree, Master's degree, doctorate or professional degree Unknown: Unknown
Smoking during the three months before or during pregnancy	Yes No Unknown
Pre-pregnancy body mass index (BMI; kg/m^2)	BMI calculated based on the mother's pre-pregnancy weight in pounds and height in feet and inches[36] (Appendix Table 3). Categorized as underweight, normal, overweight, obese, or unknown based on CDC cutoffs.
Parity	Nulliparous: 0 previous births Multiparous: ≥ 1 previous births
Gestational diabetes	Yes No Unknown
Adequacy of Prenatal Care Utilization (APNCU) Index[37]	**Inadequate/Unknown:** beginning care after the fourth month of pregnancy (16 weeks gestation) OR receiving less than 50% of expected prenatal care visits OR Unknown **Intermediate:** beginning care by the fourth month of pregnancy AND receiving 50-79% of expected visits **Adequate:** beginning care by the fourth month of pregnancy AND receiving 80-109% of expected visits **Adequate plus:** beginning care by the fourth month of pregnancy AND receiving 110% or more of expected visits. Adequate plus may indicate a problem in the pregnancy and is not necessarily indicative of good prenatal care.
Receipt of maternal WIC services	Yes No Unknown
Community socioeconomic deprivation (quartiles)	Quartiles (Q)1 – Q4 divided equally by the total number of communities in our study area Higher values of the index reflect greater community socioeconomic deprivation (Appendix Table 4 for details)

Exposure measures

Unconventional natural gas development activity

The primary exposure measure was an inverse distance-weighted index of UNGD activity[6,8,11,13,15] up to 10 miles (or 16,093.4 m) of maternal residence. We considered five buffer distances: 0.5 miles, 1 mile, 2 miles, 5 miles, and 10 miles. We included cumulative well count as a secondary measure of exposure.

There are four phases of UNGD: well pad preparation, drilling, hydraulic fracturing, and production. These phases vary in terms of duration and potential exposures. Information required to calculate the UNGD activity metric was obtained from the Pennsylvania Department of Environmental Protection (PA DEP) and Pennsylvania Department of Conservation and Natural Resources (PA DCNR).

1. **Well pad preparation -** the process of preparing a site where one or more wells are located. It is defined as the period 30 days before the first well on the pad is spudded (i.e., the day drilling begins).

2. **Drilling -** the creation of the wellbore. This phase begins on the well's spud (first drilling) date and ends on the drilling completion date.

3. **Hydraulic fracturing** (fracking, stimulation) **-** the process of injecting large volumes of water at high pressure into the wellbore to fracture the shale layer. This period is defined as beginning on the stimulation commencement date and ending on the stimulation completion date. Hydraulic fracturing may be repeated over time for a given well.

4. **Production -** the process of collecting natural gas or oil that, following hydraulic fracturing, travels through the wellbore to the surface. Production durations are variable; produced gas volume was represented as an average daily gas volume. A well was defined as being in production for reporting periods when production is indicated and reported production volume is non-zero.

The later phases of hydraulic fracturing and early stages of production can also be characterized by the generation of large amounts of spent fracking fluid and water term flowback fluid and produced water, respectively. All stages, but especially hydraulic fracturing, are also characterized by large amount truck traffic and heavy equipment that can also produce various air pollutants.

Phase-specific UNGD metrics were calculated for each birth using the following equations (Table 3).

Table 3. Definition of UNGD activity metric phase durations

Phase	Phase Name	Calculation of Phase-Specific Activity Metric
1	Well pad preparation	$\text{Phase 1 metric for birth } j = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{I_A(K)}{d_{ij}^2}$ Where: • *n* is the number of well pads within 0.5, 1, 2, 5, or 10 miles of maternal residence *j* • *k* is equal to the date of the beginning of gestation and *l* is equal to the birth date for birth *j* • $I_A(K)$ is equal to 1 when $d_{ij} \leq$ buffer distance (miles) and the phase overlaps with gestation, and is equal to 0 otherwise • d^2_{ij} is the squared distance (m^2) between well pad *i* and maternal residence *j*
2	Drilling	$\text{Phase 2 metric for birth } j = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{I_A(K)}{d_{ij}^2}$ Where: • *n* is the number of wells within 0.5, 1, 2, 5, or 10 miles of maternal residence *j* • *k* is equal to the date of the beginning of gestation and *l* is equal to the birth date for birth *j* • $I_A(K)$ is equal to 1 when $d_{ij} \leq$ buffer distance (miles) and the phase overlaps with gestation, and is equal to 0 otherwise • d^2_{ij} is the squared distance (m^2) between well *i* and maternal residence *j*
3	Hydraulic fracturing	$\text{Phase 3 metric for birth } j = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{w_i \times I_A(K)}{d_{ij}^2}$ Where: • *n* is the number of wells within 0.5, 1, 2, 5, or 10 miles of maternal residence *j* • *k* is equal to the date of the beginning of gestation and *l* is equal to the birth date for birth *j* • w_i is the depth (m) of well *i* • $I_A(K)$ is equal to 1 when $d_{ij} \leq$ buffer distance (miles) and the phase overlaps with gestation, and is equal to 0 otherwise • d^2_{ij} is the squared distance (m^2) between well *i* and maternal residence *j*
4	Production	$\text{Phase 4 metric for birth } j = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{v_i \times I_A(K)}{d_{ij}^2}$ Where: • *n* is the number of wells within 0.5, 1, 2, 5, or 10 miles of maternal residence *j*

		• k is equal to the date of the beginning of gestation and l is equal to the birth date for birth j • v_i is the produced gas volume (m^3) of well i • $I_A(K)$ is equal to 1 when $d_{ij} \leq$ buffer distance (miles) and the phase overlaps with gestation, and is equal to 0 otherwise • d^2_{ij} is the squared distance (m^2) between well i and maternal residence j

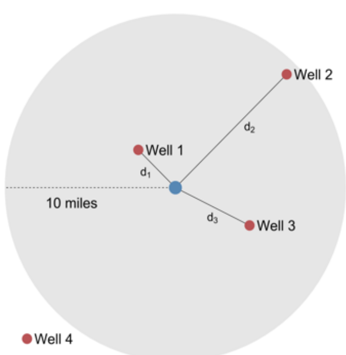
Figure 1 illustrates the calculation of the phase-specific and buffer-specific metrics.

Phase specific numerator

$$\text{Phase-specific metric for birth } j = \sum \sum \frac{\square_i}{d_{ij}^2}$$

Sum over wells i

Sum over days phase overlaps with gestation



Components of well activity metric by phase

Phase	Numerator	Denominator
Drilling	1	
Hydraulic fracturing	Well depth	Squared distance between residence and well
Production	Average daily gas volume	
Well pad construction	1	Squared distance between residence and well pad

Figure 1. Well Phase Metric Calculation

We calculated both a cumulative well count and a phase-specific activity metric for each buffer distance.

Cumulative well counts represent the number of unconventional wells spudded on or before the child's date of birth within the specified distance of the maternal residence. These counts are irrespective of time (e.g., trimester or overall gestation) and phase of unconventional well development. The counts are not inverse distance-weighted but are the total number of wells within a given buffer distance.

We defined tertiles for each exposure metric (cumulative well count, and the well pad preparation, drilling, hydraulic fracturing, and production phases) within each buffer distance (0.5, 1, 2, 5, 10 mi):

- **Unexposed**: metric = 0
- **Exposed, low**: metric >0 and metric <33.3% of non-zero values among the entire cohort
- **Exposed, moderate**: metric >0 and metric ≥ 33.3% of non-zero values and metric <66.7% of non-zero values among the entire cohort
- **Exposed, high**: metric >0 and metric ≥ 66.7% of non-zero values among the entire cohort

Births further than 10 miles from any well were considered the unexposed group for all comparisons.

Other environmental exposures
In addition to the UNGD activity index, we also considered additional sources of environmental exposures in the study area during the study period. These include additional five additional sources: three associated with oil and gas-related activity (e.g., impoundment ponds, compressor stations, facilities accepting oil and gas waste), two with other industrial activities (e.g., Toxic Release Inventory sites, Superfund National Priorities List sites), and an air quality measure.

Compressor stations. The data for compressor stations came from the PA DEP's Air Emissions Report. These data give the location of oil and gas compressor stations, pollutant types, and emissions amounts. We included the proximity of the compressor stations to residences. [PA DEP Air Quality] [PA DEP Air Emissions]

Impoundment ponds. SkyTruth is a nonprofit that uses satellite imagery and data to illustrate environmental issues. Through a multi-step review process, SkyTruth produced a map of the locations of impoundment ponds that are used to store water and other fluids from the hydraulic fracturing process. We included the proximity of the impoundment ponds to residences as a method to measure exposure. [SkyTruth]

TRI sites. The US EPA Toxics Release Inventory (TRI) tracks the management of over 650 toxic chemicals that are manufactured, processed, or otherwise used by US facilities and pose a threat to human health and the environment. Available data include reports on releases, transfers, and waste managed by each reporting facility. We included the proximity of TRI sites to residences as a method to measure exposure to general industrial activities. [TRI] [TRI Release Reports] [TRI Search]

Superfund sites. Superfund was established to allow for cleanup of hazardous waste sites, either by the US EPA or the parties responsible for the waste. Thus, proximity to Superfund sites may pose an increased risk of exposure to water, soil, or air that has been contaminated by these hazardous sites. This is particularly important in Pennsylvania as the state has the third most Superfund sites in the country. We included the proximity of Superfund sites to residences as a method to measure exposure. [Superfund] [Superfund Map] [Superfund Data and Reports] [Superfund Site Search]

Facilities accepting oil and gas waste. Waste such as drill cuttings, flowback from hydraulic fracturing, and produced water are generated during the lifecycle of a well. The disposal of these wastes may represent another potential pathway of exposure to residents, through the air, water, or soil. The PA DEP collects information from well operators about facilities where oil and gas wastes are disposed. These data include the locations of the well that generated the waste and the waste facility, the method of disposal, and the type and quantity of waste. We included proximity to facilities accepting oil and gas waste as a method to measure exposure. [PA DEP Oil and Gas] [PA DEP Waste Report] [PA DEP Waste Facilities]

We used inverse distance-weighting to quantify exposure to these five additional sources as detailed for UNGD.

Satellite imagery-based air quality monitoring. The Atmospheric Composition Analysis Group at Washington University in St. Louis satellite imagery database provides measurements of average annual and monthly particulate matter (PM) 2.5 concentrations across the US at a resolution of 1 square kilometer. PM2.5 are the fine particles that are inhalable and are regulated via ambient air quality standards for criteria pollutants. These data were used to characterize ambient exposure levels to PM 2.5 across the study area using data available from 2009 to 2017. The monthly PM2.5 values for the parcel containing the maternal residential address for 12 months prior to the month of birth were averaged to form the metric. Only births from 2010-2018 were included to align with the data availability; February – December 2018 births had less than one full year of data available in their metrics. [Atmospheric Composition Analysis Group at Washington University at St Louis]

Data Analysis

Geocoding

Geocodes (latitude and longitude) for maternal residences were provided in the birth record, along with addresses. We chose to confirm these data by geocoding all maternal residential addresses in ArcGIS (Desktop version 10.8.1.14362) using the following parameters: minimum candidate score = 70, minimum match score = 75, match if candidates tie.

If the address was not matched at least to street level, *or* if we had previously determined that the address only contained a PO box number, we used the latitude and longitude corresponding to the centroid of the intersection of the zip code tabulation area (ZCTA) and county of residence. We jittered these points by retaining the centroid latitude and longitude only to the second decimal place digits, and randomly assigning third decimal place digits (which corresponds to a distance of 111 meters) that were validated to ensure the resulting point was located within the boundaries of the ZCTA-county intersection.

Data cleaning

We examined all datasets for missing data. We computed the proportion of missing data for each variable contributing to the calculation of the UNGD activity metric, the outcome variables, and the covariates. We stratified these calculations by year to examine patterns of missingness over time.

We compared demographics of participants missing and not missing data to examine if participants missing data differ from those not missing data. Participants missing address and/or birth date information were excluded because it precluded the assignment of exposure estimates. If a participant was missing data for one or more outcomes but not all, they were included in the analysis for the non-missing outcome(s).

For the UNGD activity metric, we imputed missing well data using other available data. Missing well depths were imputed using the median value among wells with non-missing values. Missing spud dates, drilling completion dates, and stimulation dates were extrapolated using other available dates for each well and median phase durations among wells without missing dates.

We used a series of graphical analysis and descriptive statistics to identify outlying observations, implausible values, and other inconsistencies. These were handled on a case-by-case basis.

Statistical analysis

We first examined each of the four phases of the UNGD activity metric for correlation. We found no evidence that the phases were collinear (Figure 2); all phases were included in the models simultaneously.

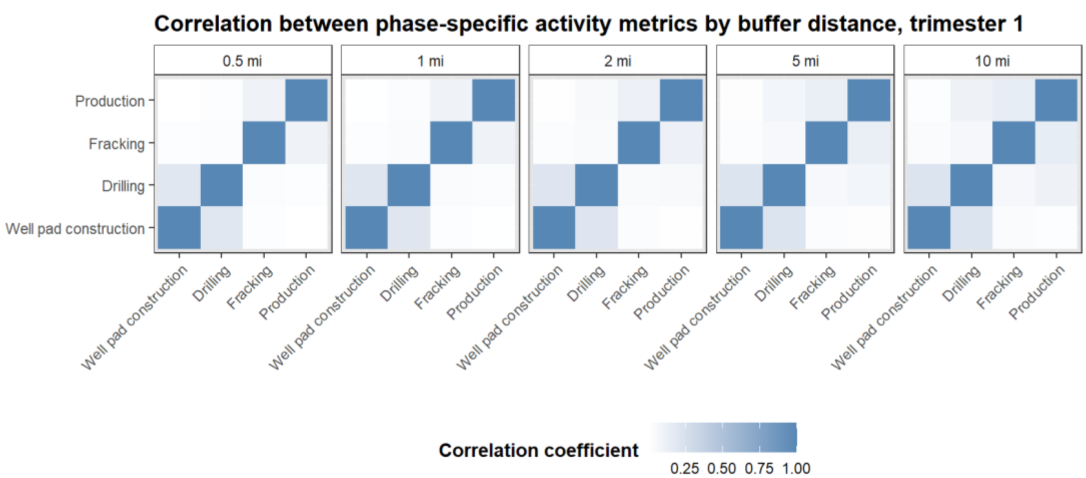


Figure 2. UNGD Phase Correlation Matrix by Buffer Distance

Phase-specific metrics were divided into tertiles among the exposed births, representing low, moderate, and high UNGD activity, respectively.

We computed descriptive statistics (for continuous variables: mean and standard deviation or median and interquartile range (IQR); for categorical variables: frequency) for outcome variables and covariates. Descriptive statistics were calculated for the entire sample as well as stratified by UNGD activity metric tertiles and, for covariates, birth outcome.

Our primary analyses assessed the association of UNGD activity metric (tertiles of exposure) with each of the four birth outcomes. We fit a series of linear (term birth weight) and logistic (preterm birth, small for gestational age, low Apgar score) regression models with clustered errors, obtained using a sandwich estimator, to account for nesting of births within mothers and of mothers within communities.

Each base model contained the four UNGD activity metrics. Our full set of covariates included neonate sex, season of birth, facility of birth, maternal age at delivery, race, ethnicity, education, smoking status three months before and during pregnancy, pre-pregnancy BMI, parity, gestational diabetes, adequacy of prenatal care, receipt of WIC services, distance to nearest roadway, community socioeconomic deprivation, greenness, and household water source.

Due to a lack of variability among our cohort in terms of ethnicity and birth facility (greater than 98% were non-Hispanic ethnicity and had hospital as the facility of birth), those two variables were not included in the models. During our checks for model fit, we identified a high proportion of records with high residuals and high leverage points and issues with model convergence, due to the inclusion of some of our environmental covariates. Additional evaluation led us to include a reduced set of covariates in all final models: neonate sex, maternal age at delivery, race, education, smoking status during pregnancy, pre-pregnancy BMI, parity, gestational diabetes, adequacy of prenatal care, receipt of WIC services, and community socioeconomic deprivation. The analysis of term birth weight was also adjusted for gestational age.

Our secondary analyses replicated the primary but included each of the five other environmental exposures (singularly) in the models.

We evaluated covariates for conditional significance using Wald or likelihood ratio tests. We assessed multicollinearity among model covariates by calculating variance inflation factors (VIF).

Associations were reported as a difference in term birth weight, or as odds ratios for preterm birth and small for gestational age. The odds ratio is used to determine whether a particular exposure (e.g., UNGD activity) is a risk factor for a particular birth outcome, and to compare the magnitude of various risk factors for that outcome. Odds ratios (OR) can be interpreted as:

OR=1 Exposure (e.g., UNGD activity) does not affect odds of the birth outcome
OR>1 Exposure (e.g., UNGD activity) is associated with higher odds of having the birth outcome
OR<1 Exposure (e.g., UNGD activity) is associated with lower odds of having the birth outcome

We compared the unexposed (reference level) to the exposed first, second, and third tertiles of the UNGD activity metric(s) with 95% confidence intervals. We used a two-sided type I error rate of 0.05 for significance testing. No adjustments were made for multiple comparisons. All analyses were performed using R version 4.1.2 (2021-11-01) and Stata 17 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC).

Results

Total Cohort Descriptive Results

The file we received from PA DOH included data for n = 257,447 births to 171,431 mothers from 2010 to 2020. Table 4 displays the numbers of births dropped for meeting each of the exclusion criteria. Births which met criteria for serious birth defects were excluded by PA DOH Vital Statistics prior to file transfer and thus the number of births meeting this criterion is unknown.

Table 4. Final Cohort Size

Exclusion Reason	No. Meeting Exclusion	Cohort Size
Serious birth defects	Unknown	257,447
Multiple birth	8,771	248,676
Missing gestational age	1,950	246,726
Pre-viability (before 22 weeks gestation)	289	246,437
Post-term (after 41 weeks gestation)	979	245,458
Birth weight <500 g	185	245,273
Residence outside of study area*	59,424	185,849

*Includes within the City of Pittsburgh

Dropping births meeting one or more exclusion criteria resulted in a final cohort of **n = 185,849 births** to 128,155 mothers.

Residence geocoding results
Most births were able to be matched to the point address (81.4%), street address (10.7%) or sub-address (which includes apartment number, suite, etc.; 6.69%) (Figure 3). Among mothers with > 1 child, the majority (n = 28,497) lived in the same community for all births. Including in the mothers with 1 child (n = 82,605), a total of 111,084 (or 86.68% of all mothers) are nested within one community. A total of 17,053 mothers with two or more children lived in at least two different communities during the study period.

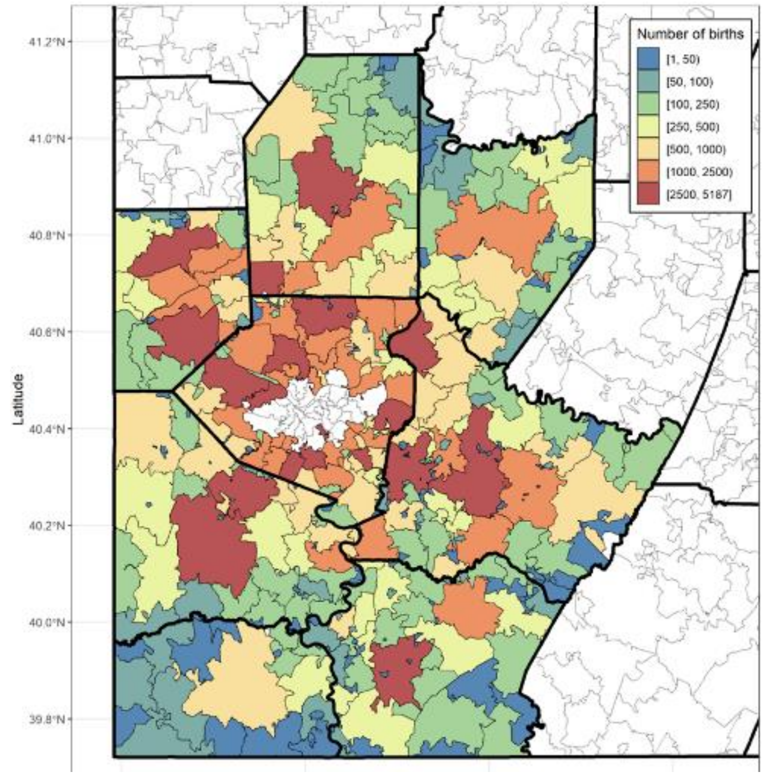


Figure 3. Map of Birth Residences by Community

Table 5 shows the count by county of number of births. Even excluding the City of Pittsburgh, Allegheny County had the highest number of births in the cohort (n=76,569, 42%), followed by Washington and Westmoreland Counties. Greene County only contributed 1% of the births to the cohort (n=2519).

Table 5. Number and Percent of Births by County

County	Number	Percent
Allegheny	76,569	42.1
Armstrong	6579	3.54
Beaver	17,322	9.32
Butler	18,185	9.78
Fayette	12,412	6.68
Greene	2519	1.36
Westmoreland	20,192	10.86
Washington	32,071	17.26

Birth outcomes
Figure 4 shows the distribution of birth weight (in grams) among term births (those with gestational age 37-41 weeks, inclusive), excluding those missing a value for birth weight.

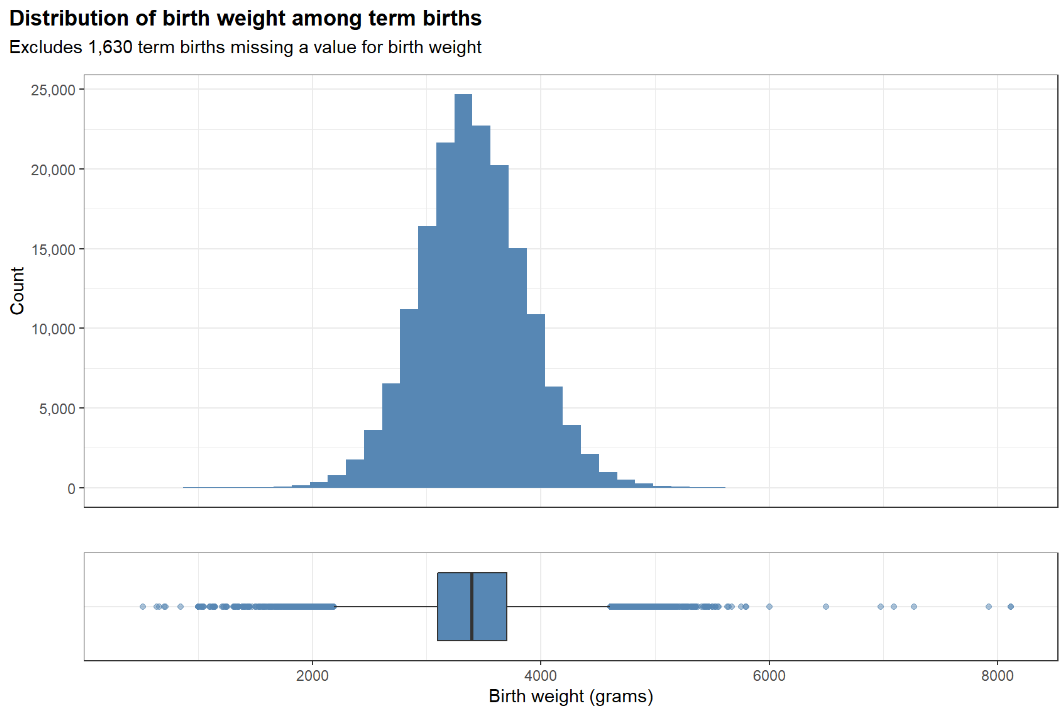


Figure 4. Histogram of Term Birthweights

	Mean	**SD**	**Median**	**Min**	**Max**
Term birthweight (g)	3402.29	463.75	3395	516	8115

Table 6 summarizes the birth outcomes in our cohort.

Table 6. Birth Outcomes in Cohort

Outcome	**N = 185,849 (%)**
Preterm (22-36 weeks gestation)	13,672 (7.4%)
Low 5-minute Apgar score	2,021 (1.1%)
Small for gestational age (SGA)	16,837 (9.2%)
Outcome	**N = 172,109 (Median; IQR[1])**
Term birth weight (grams) (37-41 weeks gestation)	3,395 (3,095, 3,700)

1- Interquartile range

Clinical and demographic covariates

There were 509 communities represented among the participants (Figure 5). The communities were divided into quartiles to form the cut points (approximately 127 communities in each quartile). Communities in Quartile 1 are those with the least deprivation and communities in Quartile 4 are those with the most deprivation. The figure shows the SDI quartile for each county, township, or census tract in the study area; those in blue (Q1) have the least deprivation while those in orange (Q4) have the highest deprivation.

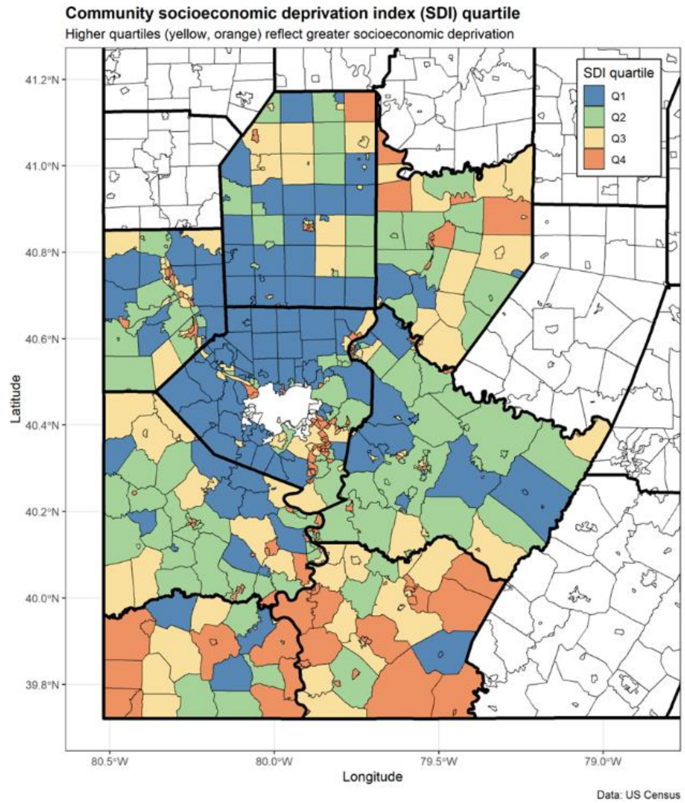


Figure 5. Map of Socioeconomic Deprivation Index by Community

Table 7 displays the number and percent of births per community socioeconomic deprivation index quartile.

Table 7. Quartiles of Socioeconomic Deprivation Index (SDI)

Community Socioeconomic Deprivation Index Quartile	Number	Percent
Quartile 1: -8.9 to <-2.77	79,409	42.8
Quartile 2: -2.77 to <-0.09	40,651	21.9
Quartile 3: -0.09 to <2.99	31,727	17.1
Quartile 4: 2.99 to <18.78	33,817	18.2

About 18% of the cohort resided in a community in the highest quartile of the SDI (Q4, most deprivation), while 43% lived in a community in the lowest quartile (Q1, least deprivation).

UNGD exposure

There were 5,799 wells included in our study from 2000 to 2020 (Figure 6). Through 2020, Washington County had the highest number of wells (n=1974), and Beaver County had the lowest number (n=141).

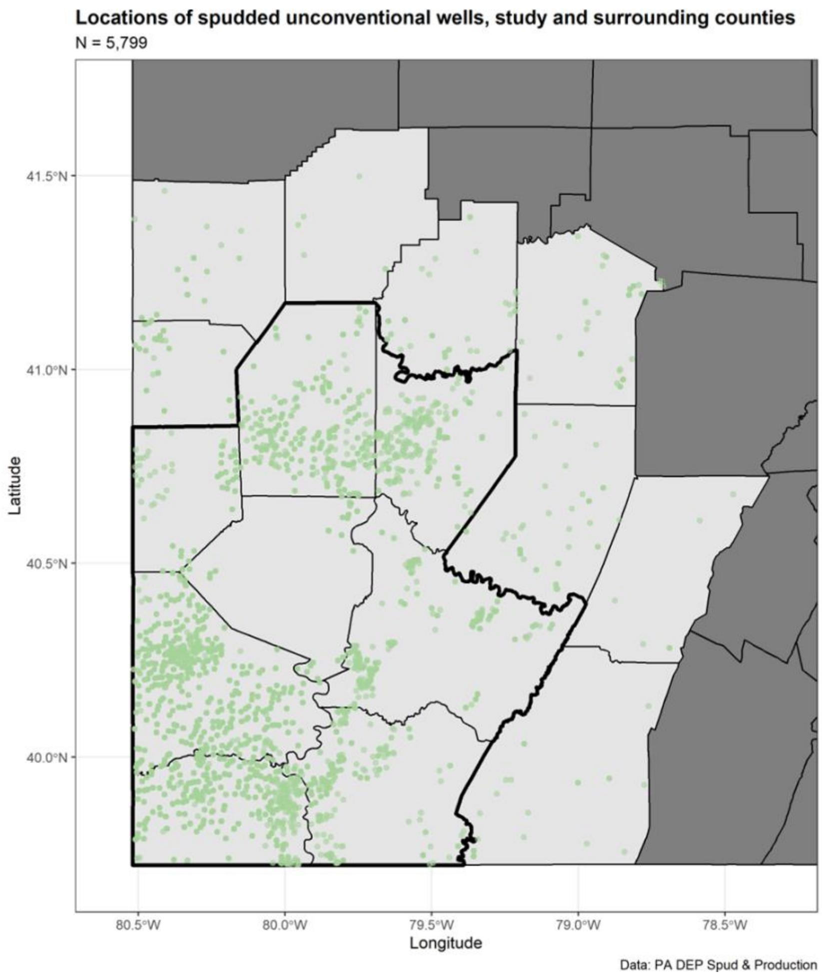


Figure 6. Map of UNGD Well Locations

There were fewer than 20 wells spudded in Southwestern Pennsylvania until 2007-2008, when production began increasing rapidly. The number of wells spudded peaked in 2014, with 765 as shown in Figure 7.

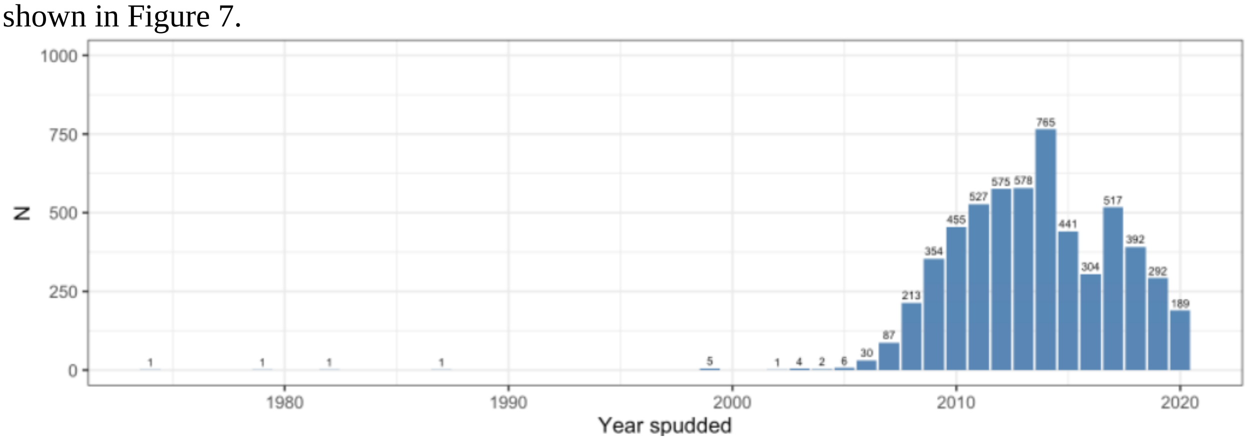


Figure 7. Histogram of UNGD Well Spud Dates by Year

Table 8 shows the median phase duration for each of the four UNGD activity metrics.

Table 8. UNGD activity metric phase durations

Phase	Phase Name	Phase Length
1	Well pad preparation	Minimum (spud date among wells on the pad) + 30 days 30 days
2	Drilling	Number of days between the spud and drilling completion dates Median: 104 days
3	Hydraulic fracturing	Number of days between stimulation commencement and stimulation completion Median: 12 days
4	Production	Duration of reporting period during which well reported production Mean: 2239 days (range 30-8769 days) Median: 2193 days

The cumulative well counts for the non-zero well counts for each buffer distance and their corresponding tertile cut points (33.3% and 66.7%) are shown in Table 9. Tertiles could not be formed for the 0.5 mi buffer because both the minimum and the 33.3% were 1.

Table 9. Cumulative Well Count Cutpoints

Exposure metric	Buffer (mi)	Min	33.3%	Median	66.7%	Max
Cumulative well count	0.5	1	1	2	3	22
	1.0	1	2	3	5	40
	2.0	1	4	7	11	114
	5.0	1	10	19	37	501
	10.0	1	39	69	111	1277

Phase- and buffer distance-specific tertile cut points (33.3% and 66.7%) for categorizing non-zero activity metrics for each buffer distance are shown in Table 10.

Table 10. Phase- and Buffer-Specific Cutpoints

Phase	Buffer (mi)	Min	33.3%	Median	66.7%	Max
Well pad preparation	0.5	0.0000016	0.0000585	0.0000714	0.0001010	3.486600e-03
	1.0	0.0000004	0.0000149	0.0000194	0.0000288	3.486600e-03
	2.0	0.0000001	0.0000041	0.0000059	0.0000093	3.497600e-03
	5.0	0.0000000	0.0000009	0.0000016	0.0000027	3.499400e-03
	10.0	0.0000000	0.0000004	0.0000007	0.0000013	3.499900e-03
Drilling	0.5	0.0000019	0.0001875	0.0003621	0.0006989	1.736130e-02
	1.0	0.0000004	0.0000471	0.0000982	0.0001985	1.736130e-02
	2.0	0.0000001	0.0000190	0.0000372	0.0000671	1.736130e-02
	5.0	0.0000000	0.0000067	0.0000136	0.0000258	1.737240e-02
	10.0	0.0000000	0.0000036	0.0000074	0.0000157	1.738150e-02
	0.5	0.0032741	0.0832197	0.1718940	0.3412145	1.353869e+01

Hydraulic fracturing	1.0	0.0005700	0.0220003	0.0473579	0.0923359	1.353869e+01
	2.0	0.0001473	0.0093184	0.0180530	0.0320462	1.353869e+01
	5.0	0.0000253	0.0032377	0.0062683	0.0119615	1.355166e+01
	10.0	0.0000063	0.0015206	0.0030728	0.0064455	1.355581e+01
Production	0.5	0.0000189	3.7609243	19.5167675	56.8160431	1.304742e+04
	1.0	0.0000074	3.4094035	12.1514347	29.8827560	1.304742e+04
	2.0	0.0000002	3.1194859	8.6408191	19.8056843	1.304742e+04
	5.0	0.0000000	1.6757591	5.1504258	13.5079528	1.308903e+04
	10.0	0.0000000	1.8369363	4.5370076	10.8305981	1.311022e+04

Table 11 shows the percentage of the birth cohort that was exposed at each buffer distance. Only about 3% of the cohort had wells within 0.5 miles of their residences. The production phase, which lasts the longest amount of time, had the highest percent exposed at each buffer distance from 2.4% at 0.5 miles to 89.4% at 10 miles. Less than 2% were exposed to the well pad preparation, drilling, or hydraulic fracturing phases at 1 mile. More than 90% of the cohort had at least one well within 10 miles of their residences.

Table 11. Percent of Cohort Exposed to UNGD Activity at Each Buffer Distance

	Buffer (miles)				
Well Metric	0.5	1	2	5	10
Cumulative well count	2.8	10.3	27.5	64.2	94.1
Well pad preparation phase	0.3	1.3	5.4	25.8	64.9
Drilling phase	0.3	1.8	8.1	35.3	76.3
Hydraulic fracturing phase	0.3	1.6	7.2	31.4	71.8
Production phase	2.4	8.9	23.8	57.9	89.4

Non-Well Exposures

We investigated modeling associations for five additional non-well exposures.

Compressor stations. We assigned inverse distance weighted activity metrics to stations that were active based on whether the facility had reported emissions during any given year (Figure 8).

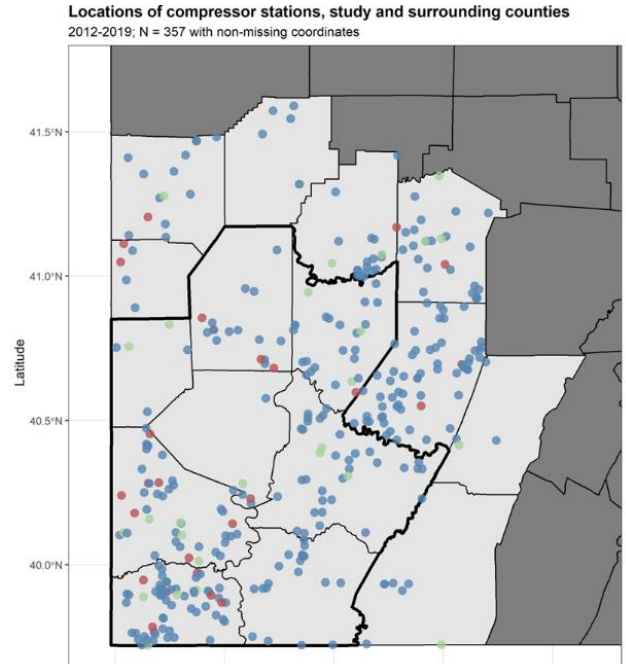


Figure 8. Locations of Study Area Compressor Stations

Impoundment ponds. We assigned inverse distance weighted activity metrics to ponds that were active based on whether the pond was visible by satellite monitoring during any given year (Figure 9).

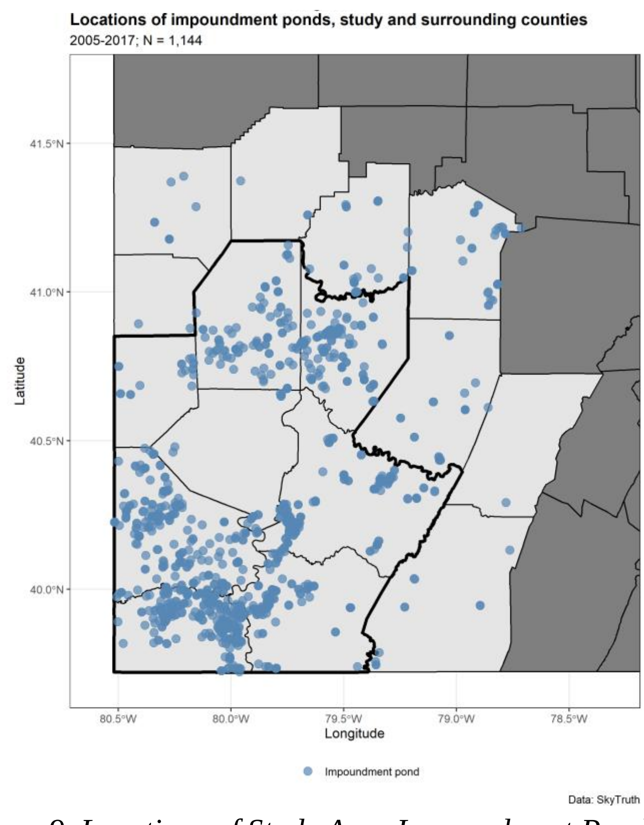


Figure 9. Locations of Study Area Impoundment Ponds

TRI sites. We assigned inverse distance weighted activity metrics to stations that were active based on whether the facility had reported emissions during any given year (Figure 10).

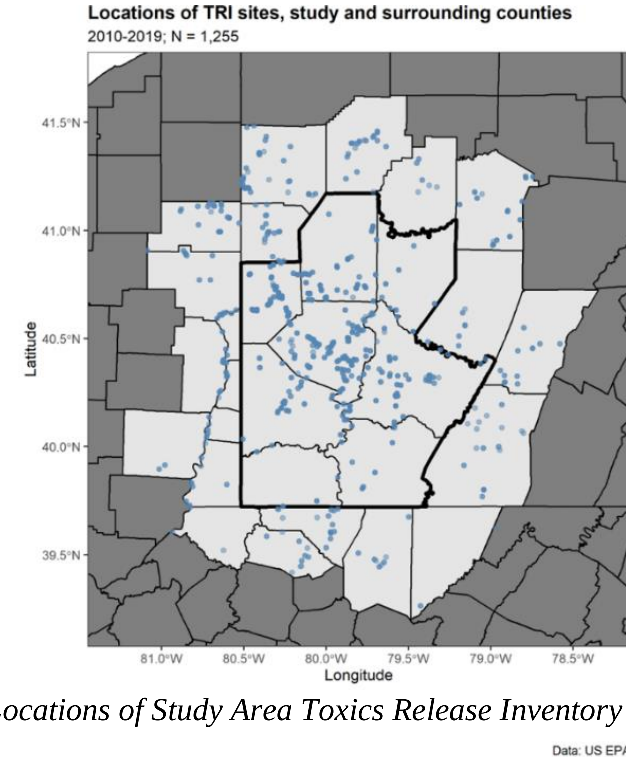


Figure 10. Locations of Study Area Toxics Release Inventory Sites

Facilities accepting oil and gas waste. We assigned inverse distance weighted activity metrics to stations that were active based on whether the facility reported accepting waste during any given year (Figure 11).

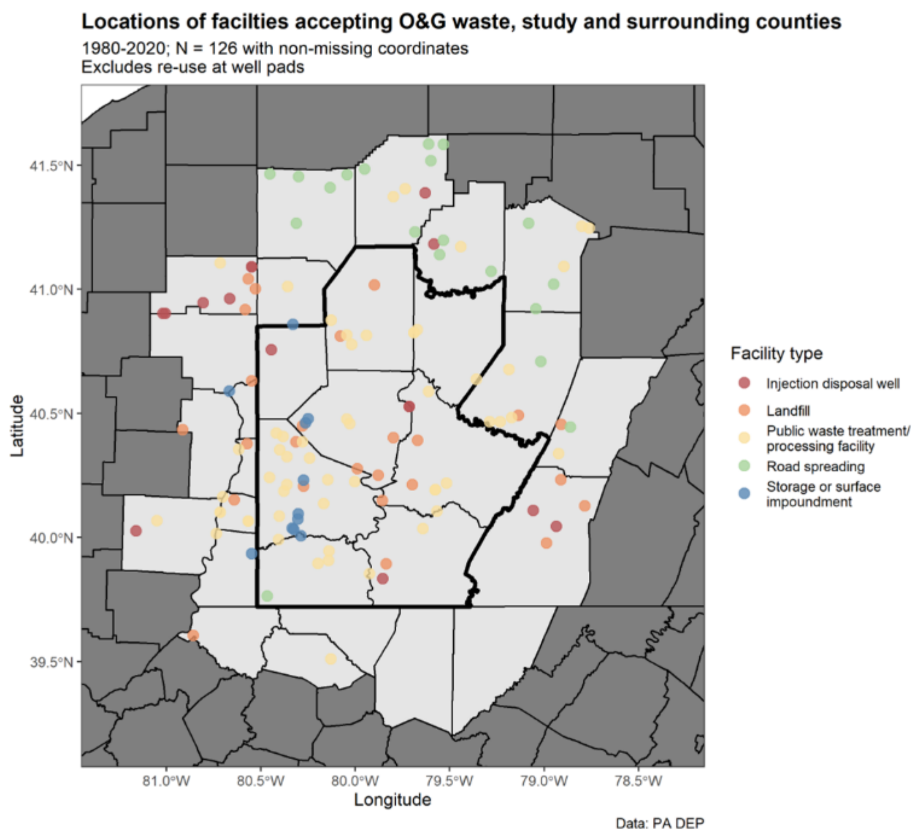


Figure 11. Locations of Study Area Facilities Accepting Oil & Gas Waste

The number of births by source within each buffer are shown in Table 12. Due to the very small number of births located within our buffer distances to Superfund sites, no additional analyses were performed using that source. Additionally, due to the high proportion of births with TRI sites within 10 miles (and correspondingly low proportion outside of 10 miles), no additional models are included due to the small baseline comparison group.

Table 12. Number of Births (Total Cohort) Within Each Buffer Distance for Non-Well Exposures

Buffer (miles)	Compressor Stations		Impoundment Ponds		Superfund Sites		TRI Sites		Facilities accepting oil & gas waste	
	Number	%	Number	%	Number	%	Number	%	Number	%
0.5	682	0.4	506	0.3	0	--	17,779	9.6	633	0.3
1	2,692	1.4	2,810	1.5	0	--	52,065	28.1	3,953	2.1
2	11,154	6.0	11,199	6.0	3	0.002	103,510	55.8	19,279	10.4
5	59,121	31.8	40,698	21.9	175	0.09	164,582	88.7	78,823	42.5
10	119,147	64.2	90,379	48.7	571	0.3	179,648	96.8	150,619	81.1

Apgar

The characteristics by low 5-minute Apgar score are shown in Table 13. Low Apgar score occurred more frequently among Black/African American mothers, those with a high school education or less, and to nulliparous and smoking mothers. A low Apgar score also occurred more frequently among those in communities with the most socioeconomic deprivation (Q4).

Table 13. Cohort Characteristics by Apgar Score Category

Characteristic	Low 5-minute Apgar Score		
	Yes, N = 2,189[1]	**No**, N = 181,731[1]	**Unknown**, N = 1,929[1]
Neonate sex			
Female	936 (42.8%)	88,874 (48.9%)	940 (48.7%)
Male	1,253 (57.2%)	92,857 (51.1%)	989 (51.3%)
Maternal age (years)[2]	29 (24, 33)	29 (25, 33)	30 (26, 33)
Gestational age (weeks)[2]	38 (34, 39)	39 (38, 40)	39 (37, 40)
Adequacy of prenatal care utilization (APNCU) index			
Inadequate	324 (14.8%)	18,919 (10.4%)	135 (7.0%)
Intermediate	207 (9.5%)	19,938 (11.0%)	96 (5.0%)
Adequate	858 (39.2%)	104,406 (57.5%)	1,350 (70.0%)
Adequate plus	600 (27.4%)	31,345 (17.2%)	208 (10.8%)
Unknown	200 (9.1%)	7123 (3.9%)	140 (7.3%)
Maternal race			
White	1,801 (82.3%)	158494 (87.2%)	1,554 (80.6%)
Black/African American	295 (13.5%)	14,585 (8.0%)	250 (13.0%)
All other races	70 (3.2%)	7,235 (4.0%)	110 (5.7%)
Unknown/refused	23 (1.1%)	1,417 (0.8%)	15 (0.8%)
Maternal education level			
Less than high school	226 (10.3%)	12,743 (7.0%)	156 (8.1%)
High school/GED	551 (25.2%)	39,261 (21.6%)	398 (20.6%)
Some college	609 (27.8%)	49,707 (27.4%)	416 (21.6%)
Bachelor's degree	480 (21.9%)	47,898 (26.4%)	571 (29.6%)
Graduate degree	290 (13.2%)	31,152 (17.1%)	357 (18.5%)
Unknown	33 (1.5%)	970 (0.5%)	31 (1.6%)
Maternal pre-pregnancy BMI			
Underweight	54 (2.5%)	4743 (2.6%)	42 (2.2%)
Normal	708 (32.3%)	69,404 (38.2%)	459 (23.8%)
Overweight	398 (18.2%)	33,685 (18.5%)	182 (9.4%)
Obese	505 (23.1%)	33,921 (18.7%)	159 (8.2%)
Unknown	524 (23.9%)	39,978 (22.0%)	1,087 (56.4%)
Gestational diabetes	149 (6.8%)	9,394 (5.2%)	59 (3.1%)
Nulliparous	1,221 (55.8%)	75,584 (41.6%)	747 (38.7%)
Mother received WIC	671 (30.7%)	50,074 (27.6%)	458 (23.7%)
Maternal smoking	545 (24.9%)	35,923 (19.8%)	305 (15.8%)
Community socioeconomic deprivation index			
Quartile 1 (least)	779 (35.6%)	77,813 (42.8%)	891 (46.2%)
Quartile 2	492 (22.5%)	39,849 (21.9%)	369 (19.1%)
Quartile 3	398 (18.2%)	31,088 (17.1%)	294 (15.2%)
Quartile 4 (most)	520 (23.8%)	32,981 (18.1%)	375 (19.4%)

[1] n (%); [2]Median (Interquartile Range (IQR))

Because low Apgar score occurred so infrequently among the births in our cohort, no additional modeling was performed.

Small for Gestational Age (SGA)

The cohort characteristics by SGA are shown in Table 14. SGA occurred more frequently among those with inadequate prenatal care, among Black/African American mothers, those with a high school education or less, and to nulliparous and smoking mothers. It also occurred more frequently among those in the highest quartile of socioeconomic deprivation.

Table 14. Cohort Characteristics by Small for Gestational Age Category

Characteristic	**Small for gestational age (SGA)**		
	Yes, N = 16,872[1]	**No**, N = 166,765[1]	**Unknown**, N = 2,212[1]
Neonate sex			
Female	8,273 (49.0%)	81,467 (48.9%)	1,010 (45.7%)
Male	8,599 (51.0%)	85,298 (51.1%)	1,202 (54.3%)
Gestational age (wks)	39 (38, 40)	39 (38, 40)	39 (37, 39)
Maternal age (years)	28 (24, 32)	29 (25, 33)	30 (26, 33)
Adequacy of prenatal care utilization (APNCU) index			
Inadequate	2,404 (14.2%)	16,925 (10.1%)	49 (2.2%)
Intermediate	1,815 (10.8%)	18,320 (11.0%)	106 (4.8%)
Adequate	9,157 (54.3%)	95,789 (57.4%)	1,668 (75.4%)
Adequate plus	2,779 (16.5%)	29,109 (17.5%)	265 (12.0%)
Unknown	717 (4.2%)	6,622 (4.0%)	124 (5.6%)
Maternal race			
White	13,393 (79.4%)	146,651 (87.9%)	1,805 (81.6%)
Black or African American	2,420 (14.3%)	12,431 (7.5%)	279 (12.6%)
All other races	913 (5.4%)	6,380 (3.8%)	122 (5.5%)
Unknown or refused	146 (0.9%)	1,303 (0.8%)	6 (0.3%)
Maternal education level			
Less than high school	2,131 (12.6%)	10,881 (6.5%)	113 (5.1%)
High school or GED	5,044 (29.9%)	34,778 (20.9%)	388 (17.5%)
Some college	4,609 (27.3%)	45,588 (27.3%)	535 (24.2%)
Bachelor's degree	3,043 (18.0%)	45,241 (27.1%)	665 (30.1%)
Graduate degree	1,951 (11.6%)	29,386 (17.6%)	462 (20.9%)
Unknown	94 (0.6%)	891 (0.5%)	49 (2.2%)
Maternal pre-pregnancy BMI			
Underweight	935 (5.5%)	3,873 (2.3%)	31 (1.4%)
Normal	6,999 (41.5%)	63,240 (37.9%)	332 (15.0%)
Overweight	2,627 (15.6%)	31,509 (18.9%)	129 (5.8%)
Obese	2,594 (15.4%)	31,860 (19.1%)	131 (5.9%)
Unknown	3,717 (22.0%)	36,283 (21.8%)	1,589 (71.8%)
Gestational diabetes	735 (4.4%)	8,829 (5.3%)	38 (1.7%)
Nulliparous	8,447 (50.1%)	68,133 (40.9%)	972 (43.9%)
Mother received WIC	6,481 (38.4%)	44,247 (26.5%)	475 (21.5%)
Maternal smoking	6,217 (36.8%)	30,306 (18.2%)	250 (11.3%)
Community socioeconomic deprivation index			
Quartile 1 (least)	5,503 (32.6%)	72,886 (43.7%)	1,094 (49.5%)
Quartile 2	3,787 (22.4%)	36,503 (21.9%)	420 (19.0%)
Quartile 3	3,151 (18.7%)	28,308 (17.0%)	321 (14.5%)
Quartile 4 (most)	4,431 (26.3%)	29,068 (17.4%)	377 (17.0%)

[1] n (%); Median (IQR)

Well Cumulative Count Models

The model results for the cumulative well count are shown in Table 15. There were no associations between cumulative well count and SGA for any of the buffer distances examined.

Table 15. SGA Birth Model Results – Well Cumulative Count Metric

Tertile Split	Adjusted OR[1] (95% CI)
0.5 miles[2]	
1 mile	
Unexposed	--
Low	0.97 (0.85, 1.10)
Moderate	0.95 (0.85, 1.06)
High	1.01 (0.90, 1.13)
Global p-value	0.23
Trend p-value	0.20
2 miles	
Unexposed	--
Low	1.07 (0.98, 1.16)
Moderate	1.02 (0.93, 1.11)
High	1.02 (0.93, 1.11)
Global p-value	0.50
Trend p-value	0.96
5 miles	
Unexposed	--
Low	1.03 (0.95, 1.11)
Moderate	1.04 (0.96, 1.12)
High	1.03 (0.95, 1.12)
Global p-value	0.91
Trend p-value	0.44
10 miles	
Unexposed	--
Low	1.02 (0.95, 1.09)
Moderate	1.01 (0.94, 1.09)
High	1.06 (0.98, 1.14)
Global p-value	0.19
Trend p-value	0.09

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during gestation and three months prior, and SDI

2- We could not use the tertile split among the exposed group for the 0.5-mile buffer because the cut points for the "exposed, low" category were [1, 1).

* p<0.05; ** p<0.001

Well Phase Activity Metric Models

Adjusted models by phase and buffer are shown in Table 16. Most of the odds ratios were at or near 1, with some exceptions. There were some statistically significantly reduced odds ratios in some metrics; the only consistent reductions were in the 10-mile buffer for well pad preparation. In the 2-to-10-mile buffers for the production phase, we found consistent, in most cases statistically significant, excesses of 10%.

Table 16. SGA Birth Model Results – Well Phase Activity Metrics

Phase	Adjusted OR[1] (95% CI)				
	0.5 miles	1 mile	2 miles	5 miles	10 miles
Well Pad Preparation					
Unexposed	--	--	--	--	--
Low	1.26 (0.59, 2.72)	0.97 (0.71, 1.32)	1.11 (0.95, 1.28)	0.95 (0.88, 1.03)	0.99 (0.94, 1.06)
Moderate	1.16 (0.56, 2.39)	1.19 (0.87, 1.64)	1.05 (0.91, 1.21)	0.96 (0.88, 1.05)	0.95 (0.89, 1.00)*
High	0.84 (0.39, 1.80)	0.91 (0.61, 1.36)	1.09 (0.94, 1.27)	0.94 (0.86, 1.02)	0.93 (0.87, 0.99)*
Global p-value	0.68	0.47	0.23	0.63	0.05
Trend p-value	0.18	0.37	0.95	0.18	0.03
Drilling					
Unexposed	--	--	--	--	--
Low	0.86 (0.43, 1.72)	1.12 (0.80, 1.55)	1.03 (0.89, 1.20)	1.00 (0.91, 1.09)	0.98 (0.92, 1.04)
Moderate	0.94 (0.47, 1.85)	0.91 (0.66, 1.25)	1.02 (0.88, 1.18)	1.03 (0.93, 1.14)	1.04 (0.96, 1.11)
High	1.39 (0.65, 2.94)	1.19 (0.87, 1.63)	1.05 (0.88, 1.24)	1.04 (0.93, 1.17)	1.03 (0.94, 1.13)
Global p-value	0.67	0.62	0.98	0.85	0.20
Trend p-value	0.45	0.29	0.28	0.49	0.39
Hydraulic Fracturing					
Unexposed	--	--	--	--	--
Low	0.76 (0.41, 1.40)	0.85 (0.63, 1.16)	0.73 (0.63, 0.84)**	0.95 (0.88, 1.03)	0.97 (0.92, 1.03)
Moderate	1.48 (0.92, 2.41)	0.72 (0.54, 0.97)*	0.87 (0.76, 1.01)	0.91 (0.83, 1.00)*	0.96 (0.90, 1.03)
High	0.88 (0.47, 1.65)	0.97 (0.73, 1.28)	0.87 (0.74, 1.01)	0.95 (0.87, 1.05)	0.97 (0.89, 1.05)
Global p-value	0.17	0.23	<0.001	0.36	0.68
Trend p-value	0.29	0.13	0.01	0.11	0.22
Production					
Unexposed	--	--	--	--	--
Low	1.05 (0.85, 1.28)	1.06 (0.94, 1.19)	1.12 (1.02, 1.22)*	1.11 (1.02, 1.20)*	1.08 (1.01, 1.16)*
Moderate	0.99 (0.80, 1.21)	0.95 (0.85, 1.07)	1.08 (0.99, 1.18)	1.11 (1.02, 1.20)*	1.09 (1.01, 1.17)*
High	1.06 (0.85, 1.32)	1.03 (0.90, 1.17)	1.08 (0.98, 1.19)	1.10 (1.01, 1.20)*	1.09 (1.01, 1.19)*
Global p-value	0.13	0.004	0.13	0.11	0.11
Trend p-value	0.24	0.38	0.43	0.04	0.03

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during gestation and three months prior, and SDI

* p<0.05; ** p<0.001

The SGA forest plots by buffer distance for each phase are shown in Figure 12. The vertical line at 1 represents a null relationship; dots below 1 indicate reduced risk and dots above 1 indicate increased risk.

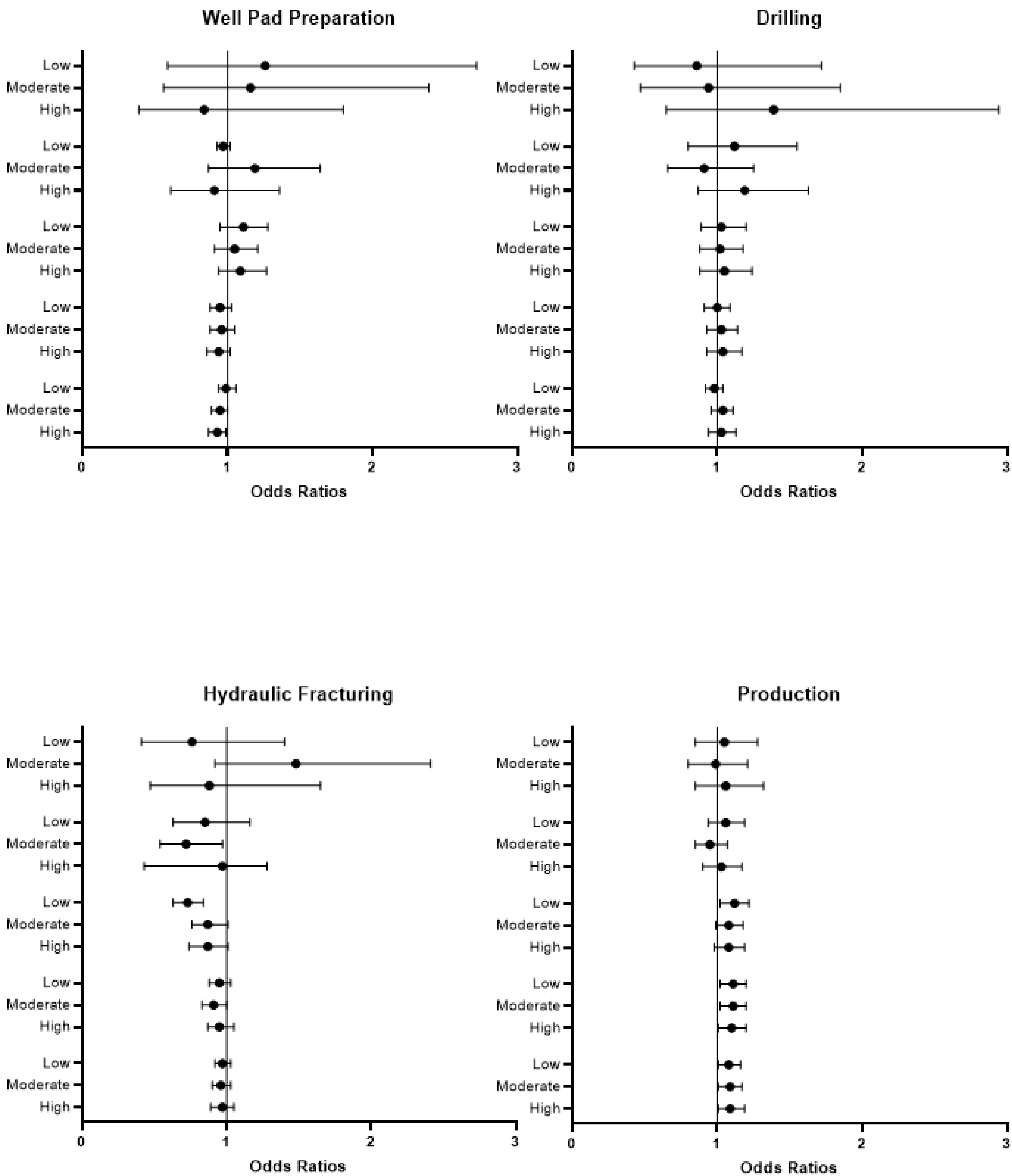


Figure 12. Forest Plots for Small for Gestational Age Well Phase Models

Non-Well Exposure Models

Table 17 shows results by buffer for compressor stations, impoundment ponds, and facilities accepting oil and gas waste. There were statistically significant elevations in the 2-, 5-, and 10-mile buffers for compressor stations, with statistically significant global tests at 2 and 5 miles. There were no consistent associations between SGA and impoundment ponds. For exposure to facilities accepting oil and gas waste, there were statistically significantly elevated odds ratios and trend tests in most of the buffer distances. The 1-mile buffer did not have any statistically significant odds ratios but was globally statistically significant.

Table 17. SGA Birth Model Results – Other Exposures

Buffer	Adjusted OR[1] (95% CI)		
	Compressor Stations	Impoundment Ponds	Facilities accepting oil & gas waste
0.5 miles			
Unexposed	--	--	--
Low	0.72 (0.42, 1.24)	1.23 (0.84, 1.82)	0.92 (0.60, 1.43)
Moderate	0.85 (0.59, 1.24)	0.89 (0.48, 1.65)	1.59 (1.05, 2.41)*
High	1.41 (1.03, 1.95)*	1.18 (0.73, 1.90)	1.28 (0.82, 2.00)
Global p-value	0.02	0.83	0.07
Trend p-value	0.01	0.96	0.01
1 mile			
Unexposed	--	--	--
Low	1.14 (0.91, 1.42)	1.01 (0.81, 1.25)	1.15 (0.96, 1.39)
Moderate	1.04 (0.84, 1.30)	0.94 (0.75, 1.18)	1.13 (0.95, 1.33)
High	0.99 (0.81, 1.22)	0.91 (0.75, 1.11)	1.21 (0.99, 1.49)
Global p-value	0.11	0.92	0.05
Trend p-value	0.02	0.58	0.003
2 miles			
Unexposed	--	--	--
Low	1.13 (1.01, 1.27)*	1.04 (0.92, 1.18)	1.01 (0.92, 1.12)
Moderate	1.13 (1.01, 1.26)*	0.91 (0.81, 1.02)	1.04 (0.96, 1.13)
High	1.08 (0.95, 1.23)	0.99 (0.88, 1.11)	1.12 (1.01, 1.23)*
Global p-value	0.02	0.56	0.07
Trend p-value	0.002	0.49	0.04
5 miles			
Unexposed	--	--	--
Low	1.02 (0.95, 1.08)	1.00 (0.93, 1.08)	1.06 (1.00, 1.12)*

Buffer	Adjusted OR[1] (95% CI)		
	Compressor Stations	Impoundment Ponds	Facilities accepting oil & gas waste
Moderate	1.01 (0.96, 1.07)	1.01 (0.94, 1.08)	1.08 (1.02, 1.14)*
High	1.09 (1.02, 1.16)*	0.99 (0.92, 1.06)	1.03 (0.98, 1.09)
Global p-value	0.03	0.99	0.12
Trend p-value	0.04	0.89	0.11
10 miles			
Unexposed	--	--	--
Low	1.05 (1.01, 1.10)*	0.99 (0.95, 1.04)	1.04 (0.99, 1.09)
Moderate	1.04 (0.99, 1.10)	1.01 (0.97, 1.06)	1.05 (1.00, 1.11)
High	1.05 (1.00, 1.10)*	0.99 (0.94, 1.04)	1.06 (1.01, 1.12)*
Global p-value	0.08	0.86	0.09
Trend p-value	0.02	0.79	0.01

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during pregnancy and three months prior, and SDI

* p<0.05; ** p<0.001

Figure 13 shows the corresponding forest plots for the associations of non-well exposures with SGA.

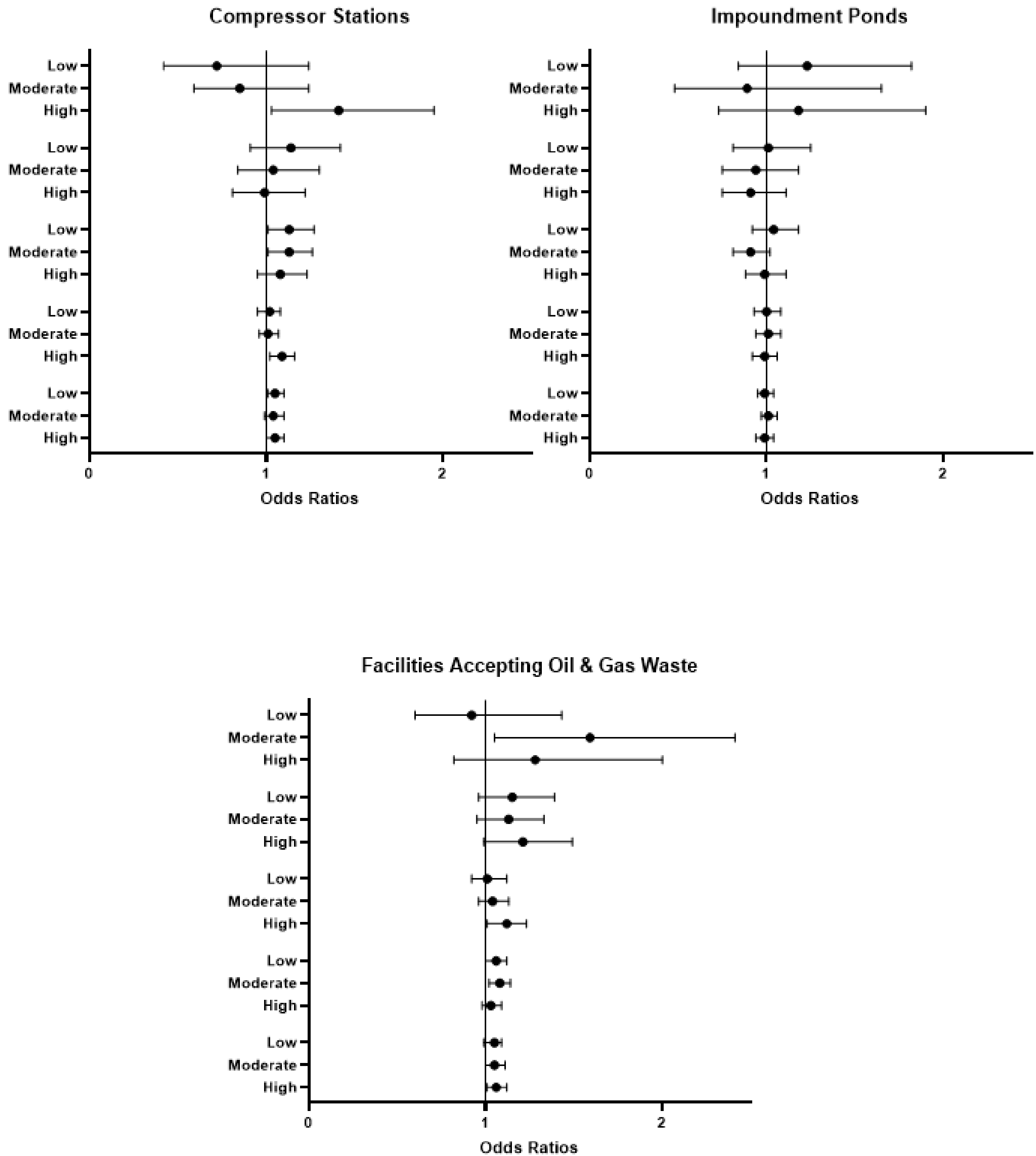


Figure 13. Forest Plots for Small for Gestational Age Non-Well Exposure Models

Preterm Birth

Preterm birth (Table 18) occurred more frequently among male neonates, those with adequate plus or unknown prenatal care, among Black/African American mothers, those with a high school education or less, and to smoking mothers. It also occurred more frequently among those in the highest quartile of socioeconomic deprivation.

Table 18. Cohort Characteristics by Preterm Birth Category

Characteristic	Preterm	
	Yes, N = 13,672[1]	**No**, N = 172,177[1]
Neonate sex		
Female	6,179 (45.2%)	84,571 (49.1%)
Male	7,493 (54.8%)	87,606 (50.9%)
Gestational age (weeks)	35 (34, 36)	39 (39, 40)
Maternal age (years)	29 (25, 33)	29 (25, 33)
Adequacy of prenatal care utilization (APNCU) index		
Inadequate	1,660 (12.1%)	17,718 (10.3%)
Intermediate	1,114 (8.1%)	19,127 (11.1%)
Adequate	4,213 (30.8%)	102,401 (59.5%)
Adequate plus	5,546 (40.6%)	26,607 (15.5%)
Unknown	1,139 (8.3%)	6,324 (3.7%)
Maternal race		
White	11,365 (83.1%)	150,484 (87.4%)
Black or African American	1,638 (12.0%)	13,492 (7.8%)
All other races	548 (4.0%)	6,867 (4.0%)
Unknown or refused	121 (0.9%)	1,334 (0.8%)
Maternal education level		
Less than high school	1,365 (10.0%)	11,760 (6.8%)
High school or GED	3,511 (25.7%)	36,699 (21.3%)
Some college	3,995 (29.2%)	46,737 (27.1%)
Bachelor's degree	2,813 (20.6%)	46,136 (26.8%)
Graduate degree	1,851 (13.5%)	29,948 (17.4%)
Unknown	137 (1.0%)	897 (0.5%)
Maternal pre-pregnancy BMI		
Underweight	483 (3.5%)	4,356 (2.5%)
Normal	4,535 (33.2%)	66,036 (38.4%)
Overweight	2,207 (16.1%)	32,058 (18.6%)
Obese	2,534 (18.5%)	32,051 (18.6%)
Unknown	3,913 (28.6%)	37,676 (21.9%)
Gestational diabetes	918 (6.7%)	8,684 (5.0%)
Nulliparous	5,970 (43.7%)	71,582 (41.6%)
Mother received WIC	4,210 (30.8%)	46,993 (27.3%)
Maternal smoking	3,528 (25.8%)	33,245 (19.3%)
Community socioeconomic deprivation index		
Quartile 1 (lowest deprivation)	4,884 (35.7%)	74,599 (43.3%)
Quartile 2	3,050 (22.3%)	37,660 (21.9%)
Quartile 3	2,472 (18.1%)	29,308 (17.0%)
Quartile 4 (highest deprivation)	3,266 (23.9%)	30,610 (17.8%)

[1] n (%); Median (IQR)

Well Cumulative Count Models

The adjusted model results for the cumulative well count are shown in Table 19. All of the odds ratios were less than 1 and most were statistically significant, including all those in the 2-, 5- and 10-mile buffers. All global and the 10-mile trend test were statistically significant.

Table 19. Preterm Birth Model Results – Well Cumulative Count Metric

Tertile Split	Adjusted OR[1] (95% CI)
0.5 miles[2]	
1 mile	
Unexposed	--
Low	0.95 (0.85, 1.06)
Moderate	0.85 (0.76, 0.96)*
High	0.92 (0.82, 1.03)
Global p-value	<0.001
Trend p-value	0.82
2 miles	
Unexposed	--
Low	0.83 (0.76, 0.91)**
Moderate	0.90 (0.82, 0.99)*
High	0.91 (0.83, 0.98)*
Global p-value	<0.001
Trend p-value	0.81
5 miles	
Unexposed	--
Low	0.85 (0.79, 0.92)**
Moderate	0.85 (0.79, 0.92)**
High	0.90 (0.83, 0.98)*
Global p-value	<0.001
Trend p-value	0.64
10 miles	
Unexposed	--
Low	0.88 (0.82, 0.94)**
Moderate	0.86 (0.80, 0.92)**
High	0.87 (0.80, 0.93)**
Global p-value	<0.001
Trend p-value	0.02

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during gestation and three months prior, and SDI

2- We could not use the tertile split among the exposed group for the 0.5-mile buffer because the cut points for the “exposed, low” category were [1, 1).

* p<0.05; ** p<0.001

Well Phase Activity Metric Models

Adjusted models by phase and buffer are shown in Table 20. There was no evidence of increased risk for the well pad preparation and hydraulic fracturing phases. There were statistically significant elevations in risk for the drilling phase in the 2- and 10-mile buffers that increased with increased exposure; however, the odds ratios in the 5-mile buffer were elevated but not statistically significant. Most of the odds ratios for the production phase were at or near 1, although there were some statistically significantly reduced odds ratios in the 5- and 10-mile buffers with statistically significant global and trend tests.

Table 20. Preterm Birth Model Results – Well Phase Activity Metrics

Phase	Adjusted OR[1] (95% CI)				
	0.5 miles	1 mile	2 miles	5 miles	10 miles
Well Pad Preparation					
Unexposed	--	--	--	--	--
Low	0.52 (0.17, 1.66)	1.04 (0.73, 1.51)	1.00 (0.85, 1.18)	0.94 (0.85, 1.03)	0.95 (0.89, 1.01)
Moderate	0.89 (0.41, 1.92)	1.08 (0.75, 1.57)	0.94 (0.78, 1.12)	0.92 (0.83, 1.03)	0.90 (0.83, 0.97)*
High	0.56 (0.20, 1.59)	0.74 (0.50, 1.09)	0.86 (0.70, 1.05)	0.95 (0.85, 1.07)	0.96 (0.88, 1.05)
Global p-value	0.54	0.34	0.37	0.55	0.03
Trend p-value	0.31	0.33	0.18	0.67	0.46
Drilling					
Unexposed	--	--	--	--	--
Low	1.09 (0.39, 3.03)	0.99 (0.72, 1.38)	1.13 (0.93, 1.36)	1.05 (0.94, 1.18)	1.05 (0.97, 1.14)
Moderate	1.08 (0.55, 2.13)	1.12 (0.79, 1.59)	1.25 (1.04, 1.50)*	1.08 (0.96, 1.22)	1.10 (1.01, 1.21)*
High	1.03 (0.51, 2.11)	0.93 (0.65, 1.32)	1.22 (1.00, 1.47)*	1.14 (0.99, 1.31)	1.12 (1.00, 1.26)*
Global p-value	0.99	0.84	0.15	0.42	0.18
Trend p-value	0.99	0.88	0.02	0.13	0.17
Hydraulic Fracturing					
Unexposed	--	--	--	--	--
Low	1.33 (0.60, 2.95)	1.02 (0.69, 1.49)	0.99 (0.83, 1.17)	1.06 (0.96, 1.17)	1.02 (0.96, 1.09)
Moderate	0.46 (0.22, 0.97)*	1.04 (0.79, 1.37)	0.89 (0.74, 1.07)	0.95 (0.86, 1.05)	0.99 (0.92, 1.07)
High	0.72 (0.36, 1.42)	0.82 (0.60, 1.12)	0.87 (0.74, 1.03)	0.98 (0.88, 1.10)	1.02 (0.93, 1.12)
Global p-value	0.19	0.76	0.47	0.22	0.66
Trend p-value	0.50	0.48	0.08	0.49	0.87
Production					
Unexposed	--	--	--	--	--
Low	1.01 (0.85, 1.20)	1.03 (0.89, 1.19)	0.96 (0.88, 1.05)	0.96 (0.88, 1.03)	1.00 (0.92, 1.07)
Moderate	0.96 (0.79, 1.17)	0.94 (0.83, 1.06)	0.91 (0.82, 1.01)	0.88 (0.81, 0.96)*	0.82 (0.76, 0.89)**

Phase	Adjusted OR[1] (95% CI)				
	0.5 miles	1 mile	2 miles	5 miles	10 miles
High	1.05 (0.84, 1.32)	0.84 (0.73, 0.97)*	0.86 (0.77, 0.95)*	0.82 (0.75, 0.90)**	0.79 (0.72, 0.86)**
Global p-value	0.01	0.004	0.01	<0.001	<0.001
Trend p-value	0.43	0.21	0.10	<0.001	<0.001

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during gestation and three months prior, and SDI

* p<0.05; ** p<0.001

The preterm birth forest plots by buffer distance for each phase are shown in Figure 14. The vertical line at 1 represents a null relationship; dots below 1 indicate reduced risk and dots above 1 indicate increased risk.

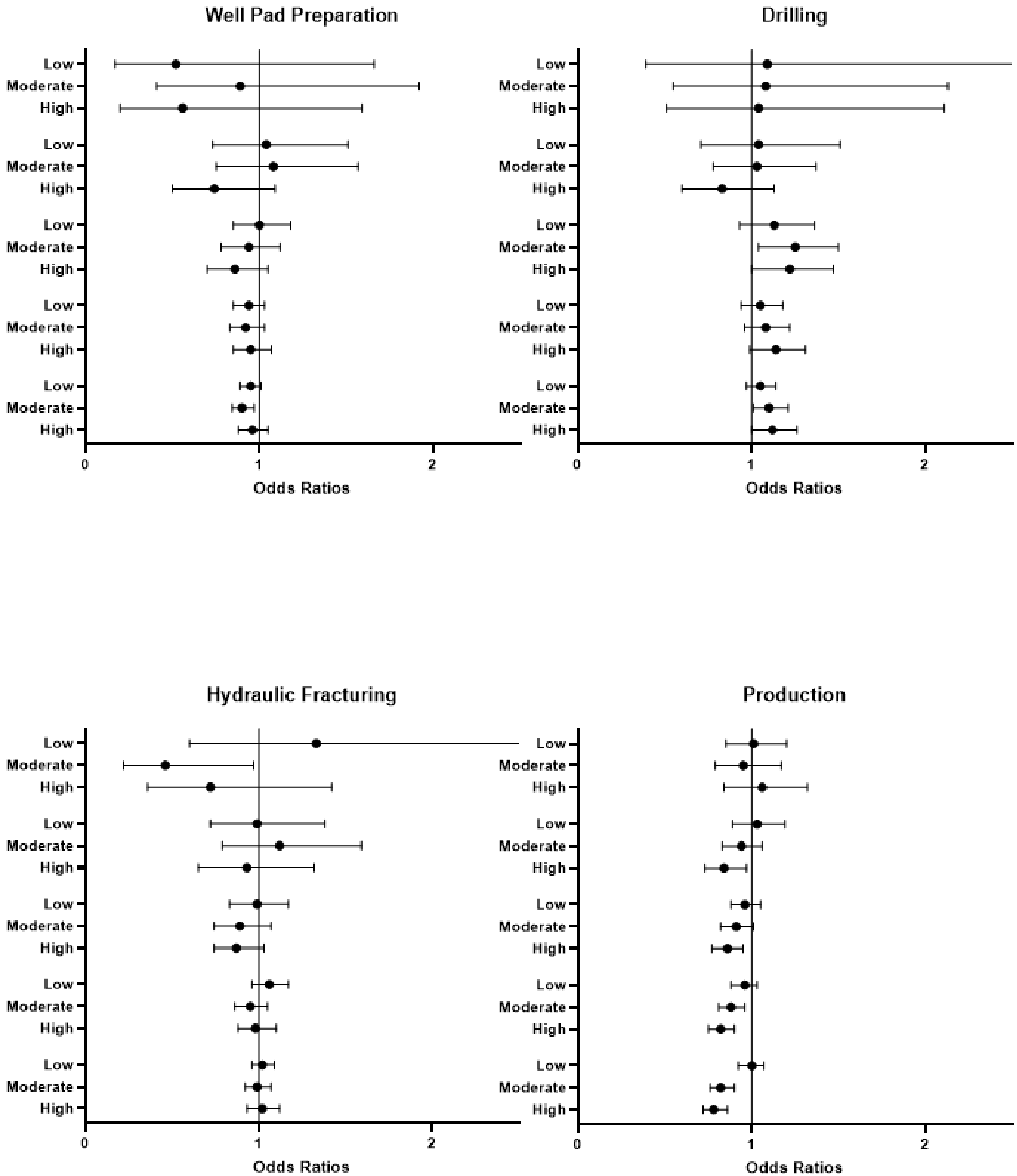


Figure 14. Forest Plots for Preterm Birth Models

Non-Well Exposure Models

Table 21 shows results by buffer for compressor stations, impoundment ponds, and facilities accepting oil and gas waste. There was no indication of increased risk of preterm birth for any of the facilities; many of odds ratios were at 1 or reduced, and many were statistically significant with significant global and trend tests.

Table 21. Preterm Birth Model Results – Other Exposures

Buffer	Adjusted OR[1] (95% CI)		
	Compressor Stations	Impoundment Ponds	Facilities accepting oil & gas waste
0.5 miles			
Unexposed	--	--	--
Low	0.78 (0.50, 1.21)	0.81 (0.47, 1.38)	1.14 (0.70, 1.87)
Moderate	0.56 (0.33, 0.95)*	1.41 (0.77, 2.58)	1.04 (0.63, 1.72)
High	0.78 (0.45, 1.37)	0.80 (0.39, 1.64)	0.68 (0.37, 1.25)
Global p-value	<0.001	0.50	<0.001
Trend p-value	<0.001	0.48	<0.001
1 mile			
Unexposed	--	--	--
Low	0.99 (0.74, 1.33)	1.17 (0.89, 1.53)	0.87 (0.69, 1.10)
Moderate	0.80 (0.59, 1.10)	0.96 (0.74, 1.24)	0.88 (0.71, 1.09)
High	0.79 (0.60, 1.04))	1.07 (0.82, 1.39)	0.89 (0.73, 1.08)
Global p-value	<0.001	0.73	<0.001
Trend p-value	<0.001	0.40	<0.001
2 miles			
Unexposed	--	--	--
Low	0.89 (0.78, 1.02)	1.03 (0.88, 1.21)	0.86 (0.77, 0.96)*
Moderate	0.82 (0.70, 0.95)*	1.05 (0.92, 1.21)	0.84 (0.76, 0.94)*
High	0.90 (0.77, 1.06)	1.12 (0.99, 1.27)	0.88 (0.79, 0.98)*
Global p-value	<0.001	0.49	<0.001
Trend p-value	<0.001	0.12	0.003
5 miles			
U.9nexposed	--	--	--
Low	0.91 (0.83, 0.98)*	1.00 (0.93, 1.08)	0.87 (0.81, 0.93)**
Moderate	0.89 (0.83, 0.96)*	1.09 (1.00, 1.18)*	0.81 (0.76, 0.87)**
High	0.88 (0.82, 0.95)**	1.09 (1.00, 1.19)*	0.85 (0.78, 0.91)**
Global p-value	<0.001	0.08	<0.001
Trend p-value	0.001	0.02	<0.001
10 miles			
Unexposed	--	--	--

Buffer	Adjusted OR[1] (95% CI)		
	Compressor Stations	Impoundment Ponds	Facilities accepting oil & gas waste
Low	0.94 (0.88, 1.00)	0.95 (0.90, 1.01)	0.89 (0.84, 0.94)**
Moderate	0.87 (0.82, 0.92)**	1.01 (0.95, 1.06)	0.85 (0.80, 0.90)**
High	0.89 (0.83, 0.95)**	1.09 (1.03, 1.16)*	0.81 (0.76, 0.86)**
Global p-value	<0.001	0.01	<0.001
Trend p-value	<0.001	0.04	<0.001

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during pregnancy and three months prior, and SDI

* p<0.05; ** p<0.001

The preterm birth forest plots for the non-well exposures are shown in Figure 15.

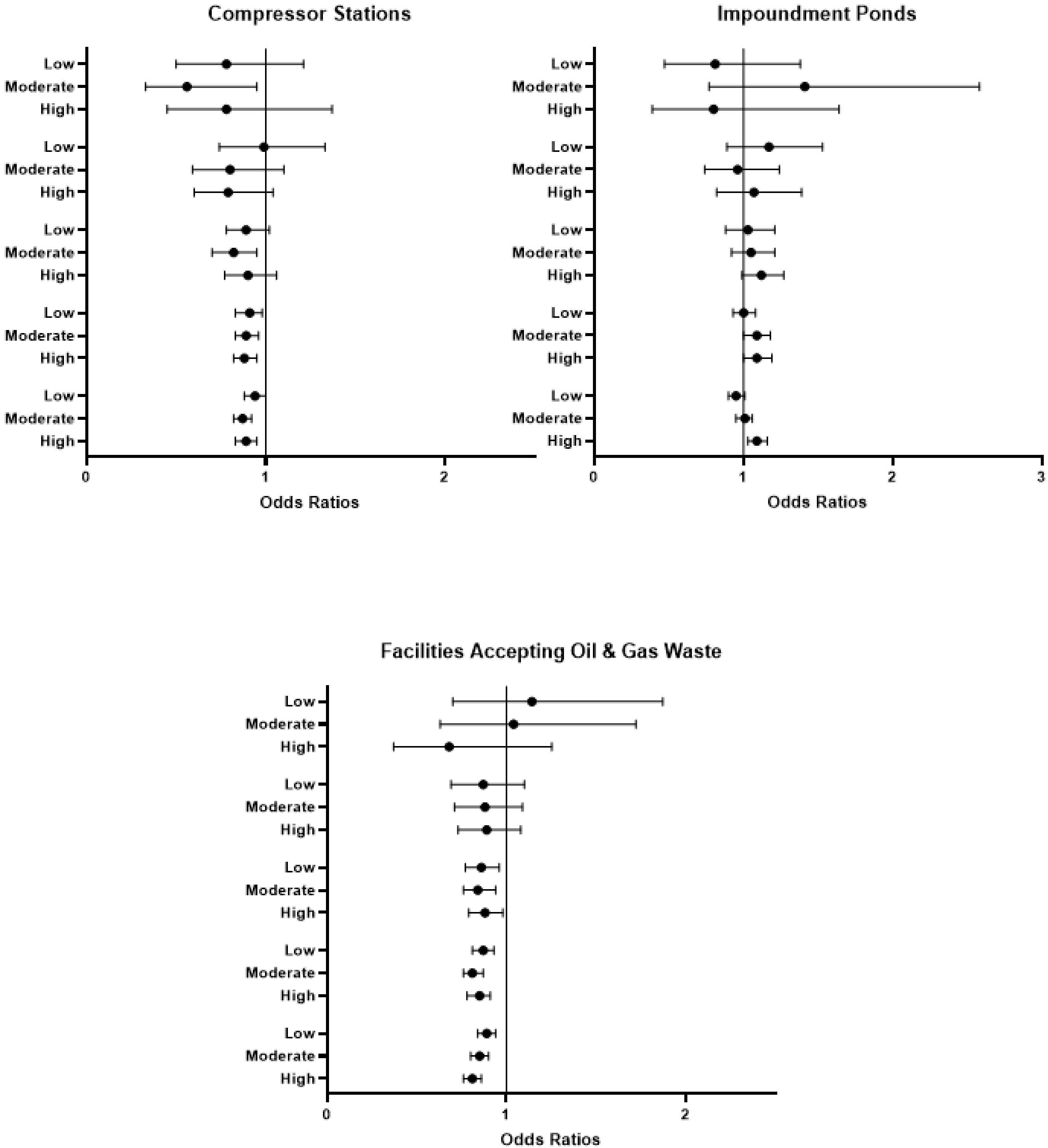


Figure 15. Forest Plots for Preterm Birth Non-Well Exposure Models

Term Birthweight

Term births were defined as those with gestational age between 37-41 weeks, inclusive. There were 170,479 births (37-41 weeks gestational age) with birthweight information available.

Well Cumulative Count Models

Table 22 below shows adjusted models for changes in term birthweight by buffer. In general, there were small, not statistically significant differences in birthweight using the cumulative count metric, although the Exposed, moderate metric had a statistically significantly elevated weight in the 1-mile buffer. The 10-mile buffer was statistically significant globally and the Exposed, high metric had a statistically significantly reduced weight.

Table 22. Term Birthweight (grams) Model Results – Well Cumulative Count Metric

Buffer	Adjusted Term Birthweight (grams)[1] (95% CI)
0.5 miles[2]	
1 mile	
Unexposed	--
Low	-6.29 (-23.61, 11.03)
Moderate	4.10 (-10.30, 18.50)
High	-14.12 (-31.80, 3.55)
Global p-value	0.12
Trend p-value	0.58
2 miles	
Unexposed	--
Low	-5.07 (-18.39, 8.25)
Moderate	-2.06 (-15.64, 11.52)
High	-11.70 (-25.49, 2.09)
Global p-value	0.27
Trend p-value	0.42
5 miles	
Unexposed	--
Low	-6.44 (-18.82, 5.94)
Moderate	-8.20 (-20.42, 4.03)
High	-8.49 (-20.87, 3.89)
Global p-value	0.65
Trend p-value	0.14
10 miles	
Unexposed	--
Low	-0.68 (-12.14, 10.78)
Moderate	-8.02 (-20.15, 4.10)
High	-12.40 (-24.47, -0.32)*
Global p-value	0.002
Trend p-value	0.002

1- Models adjusted for gestational age, neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during gestation and three months prior, and SDI

2- We could not use the tertile split among the exposed group for the 0.5-mile buffer because the cut points for the "exposed, low" category were [1, 1).

* p<0.05; ** p<0.001

Well Phase Activity Metric Models

Adjusted phase and buffer-specific model results for term birthweight are shown in Table 23. Across all buffers, there were consistent, statistically significant reductions in birthweight for the production phase. For well pad preparation, there were increases in birthweight which were statistically significant at the 5- and 10-mile buffers. There were no consistent relationships for the drilling and hydraulic fracturing phases.

Table 23. Term Birthweight (grams) Model Results – Well Phase Activity Metrics

Phase	Adjusted[1] Term Birthweight (grams) (95% CI)				
	0.5 miles	1 mile	2 miles	5 miles	10 miles
Well Pad Preparation					
Unexposed	--	--	--	--	--
Low	-18.27 (-103.00, 66.46)	23.80 (-15.77, 63.36)	15.14 (-4.96, 35.24)	17.97 (8.26, 27.68)**	7.92 (0.52, 15.31)*
Moderate	-44.23 (-135.75, 47.30)	1.40 (-36.20, 39.00)	3.11 (-16.13, 22.35)	19.74 (8.43, 31.05)**	13.97 (6.82, 21.12)**
High	3.30 (-74.36, 80.96)	25.35 (-12.69, 63.38)	5.36 (-14.70, 25.43)	23.16 (11.47, 34.84)**	27.28 (18.22, 36.35)**
Global p-value	0.002	<0.001	0.002	<0.001	<0.001
Trend p-value	<0.001	<0.001	0.004	<0.001	<0.001
Drilling					
Unexposed	--	--	--	--	--
Low	14.63 (-70.91, 100.17)	-13.00 (-55.59, 29.60)	-2.53 (-21.68, 16.62)	-4.02 (-15.77, 7.74)	2.91 (-4.99, 10.82)
Moderate	-11.97 (-79.66, 55.71)	-18.24 (-51.92, 15.44)	-4.54 (-23.52, 14.45)	-0.93 (-14.44, 12.58)	-5.80 (-15.34, 3.74)
High	-13.54 (-101.24, 74.16)	-28.45 (-70.58, 13.69)	-17.71 (-37.54, 2.11)	-5.05 (-19.28, 9.18)	-8.22 (-20.78, 4.35)
Global p-value	0.93	0.73	0.46	0.85	0.06
Trend p-value	0.17	0.03	0.02	0.73	0.10
Hydraulic Fracturing					
Unexposed	--	--	--	--	--
Low	43.99 (-29.25, 117.23)	15.83 (-17.52, 49.18)	32.23 (15.63, 48.83)**	5.17 (-3.90, 14.25)	5.05 (-1.29, 11.39)
Moderate	12.64 (-52.09, 77.38)	17.22 (-10.41, 44.85)	3.42 (-11.56, 18.40)	5.79 (-3.99, 15.57)	0.68 (-6.53, 7.88)
High	-0.36 (-73.51, 72.79)	5.04 (-26.74, 36.82)	19.48 (3.02, 35.94)*	0.75 (-9.48, 10.98)	1.49 (-7.39, 10.36)
Global p-value	0.69	0.67	<0.001	0.62	0.34
Trend p-value	0.31	0.19	0.004	0.63	0.64
Production					
Unexposed	--	--	--	--	--
Low	-24.71 (-51.60, 2.19)	-16.65 (-32.29, -1.02)*	-14.74 (-27.55, -1.93)*	-19.61 (-30.13, -9.09)**	-13.49 (-23.17, -3.82)*
Moderate	-16.55 (-43.97, 10.87)	-4.30 (-18.68, 10.09)	-18.13 (-30.71, -5.55)*	-19.89 (-30.93, -8.84)**	-17.47 (-27.82, -7.13)**
High	-16.54 (-46.77, 13.69)	-19.67 (-36.03, -3.31)*	-23.37 (-35.83, -10.91)**	-26.50 (-37.94, -15.07)**	-21.47 (-32.58, -10.37)**

Phase	Adjusted[1] Term Birthweight (grams) (95% CI)				
	0.5 miles	1 mile	2 miles	5 miles	10 miles
Global p-value	0.01	<0.001	0.004	<0.001	0.002
Trend p-value	0.01	0.22	0.02	<0.001	<0.001

1- Models adjusted for gestational age, neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during gestation and three months prior, and SDI

* p<0.05; ** p<0.001

The term birthweight forest plots by buffer distance for each phase are shown in Figure 16. The vertical line at 0 represents no change in term birthweight (grams); dots below 0 indicate reduced term birthweight and dots above 0 indicate increased term birthweight.

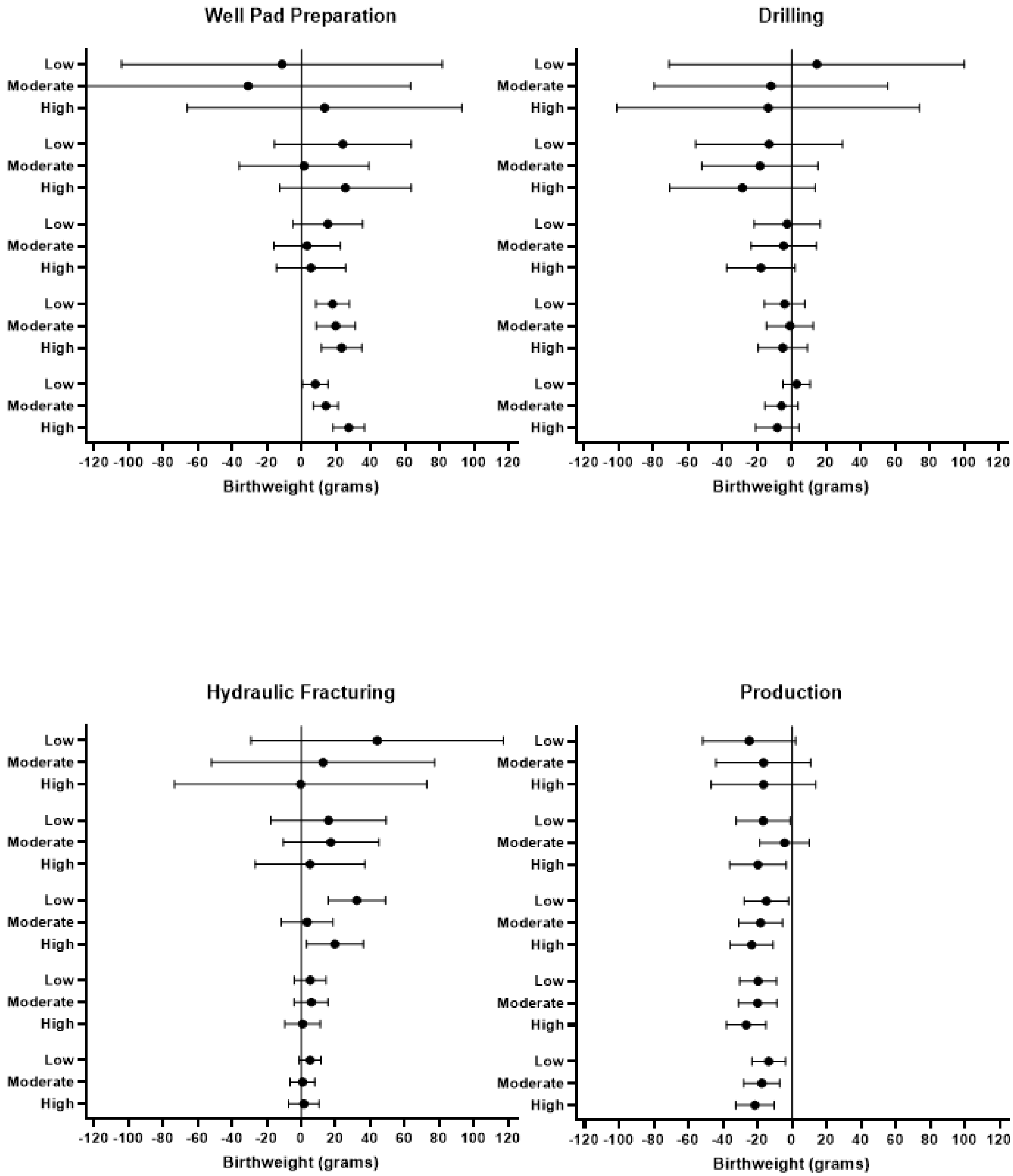


Figure 16. Forest Plots for Term Birthweight Models

Non-Well Exposure Models

Table 24 shows results by buffer for the non-well exposures. For compressor stations, we found reduced birthweights for nearly all tertiles in all buffers, many of which were statistically significant, with corresponding statistically significant global and trend tests. We found no consistent association with exposure to impoundment ponds. There were statistically significant reductions in birthweight for facilities accepting oil and gas waste in each buffer, many of which were statistically significant, with corresponding statistically significant global and trend tests.

Table 24. Term Birthweight (grams) Model Results – Other Exposures

Buffer	Adjusted[1] Term Birthweight (grams) (95% CI)		
	Compressor Stations	Impoundment Ponds	Facilities accepting oil & gas waste
0.5 miles			
Unexposed	--	--	--
Low	-21.68 (-87.11, 43.76)	-33.86 (-102.31, 34.60)	5.61 (-62.79, 74.01)
Moderate	-89.38 (-133.63, -45.12)**	5.78 (-59.22, 70.78)	-71.44 (-116.11, -26.76)*
High	-15.24 (-71.84, 41.36)	-10.52 (-59.32, 38.29)	-6.70 (-70.66, 57.25)
Global p-value	<0.001	0.46	<0.001
Trend p-value	<0.001	0.23	<0.001
1 mile			
Unexposed	--	--	--
Low	-23.10 (-52.04, 5.84)	-14.62 (-39.63, 10.39)	-51.35 (-75.10, -27.60)**
Moderate	-7.29 (-32.40, 17.82)	27.84 (-0.41, 56.09)	-41.42 (-66.90, -15.94)**
High	-36.98 (-63.60, -10.37)*	8.08 (-15.69, 31.85)	-33.08 (-55.80, -10.37)*
Global p-value	<0.001	0.17	<0.001
Trend p-value	<0.001	0.11	<0.001
2 miles			
Unexposed	--	--	--
Low	-20.52 (-35.43, -5.61)*	2.21 (-11.65, 16.07)	-14.72 (-28.44, -1.00)*
Moderate	-26.22 (-44.01, -8.43)*	20.06 (4.88, 35.24)*	-7.03 (-19.15, 5.09)
High	-28.56 (-46.12, -11.00)*	2.32 (-11.70, 16.34)	-37.37 (-50.34, -24.39)**
Global p-value	<0.001	0.12	<0.001
Trend p-value	<0.001	0.08	<0.001
5 miles			
Unexposed	--	--	--
Low	-12.22 (-19.24, -5.20)**	1.74 (-7.30, 10.77)	-21.76 (-28.89, -14.63)**

Buffer	Adjusted[1] Term Birthweight (grams) (95% CI)		
	Compressor Stations	Impoundment Ponds	Facilities accepting oil & gas waste
Moderate	-9.45 (-17.81, -1.10)*	4.39 (-3.98, 12.76)	-17.23 (-24.91, -9.55)**
High	-22.76 (-31.90, -13.62)**	5.01 (-4.00, 14.03)	-20.51 (-28.67, -12.35)**
Global p-value	<0.001	0.66	<0.001
Trend p-value	<0.001	0.16	<0.001
10 miles			
Unexposed	--	--	--
Low	-13.42 (-20.08, -6.76)**	-0.09 (-6.03, 5.86)	-12.85 (-18.88, -6.82)**
Moderate	-16.34 (-23.39, -9.29)**	3.41 (-3.00, 9.81)	-20.78 (-27.39, -14.17)**
High	-16.92 (-23.94, -9.89)**	5.87 (-0.27, 12.00)	-21.76 (-28.55, -14.98)**
Global p-value	<0.001	0.24	<0.001
Trend p-value	<0.001	0.07	<0.001

1- Models adjusted for neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, receipt of WIC services, gestational diabetes, parity, smoking during pregnancy and three months prior, and SDI

* p<0.05; ** p<0.001

The forest plots for term birthweight non-well exposures are shown in Figure 17.

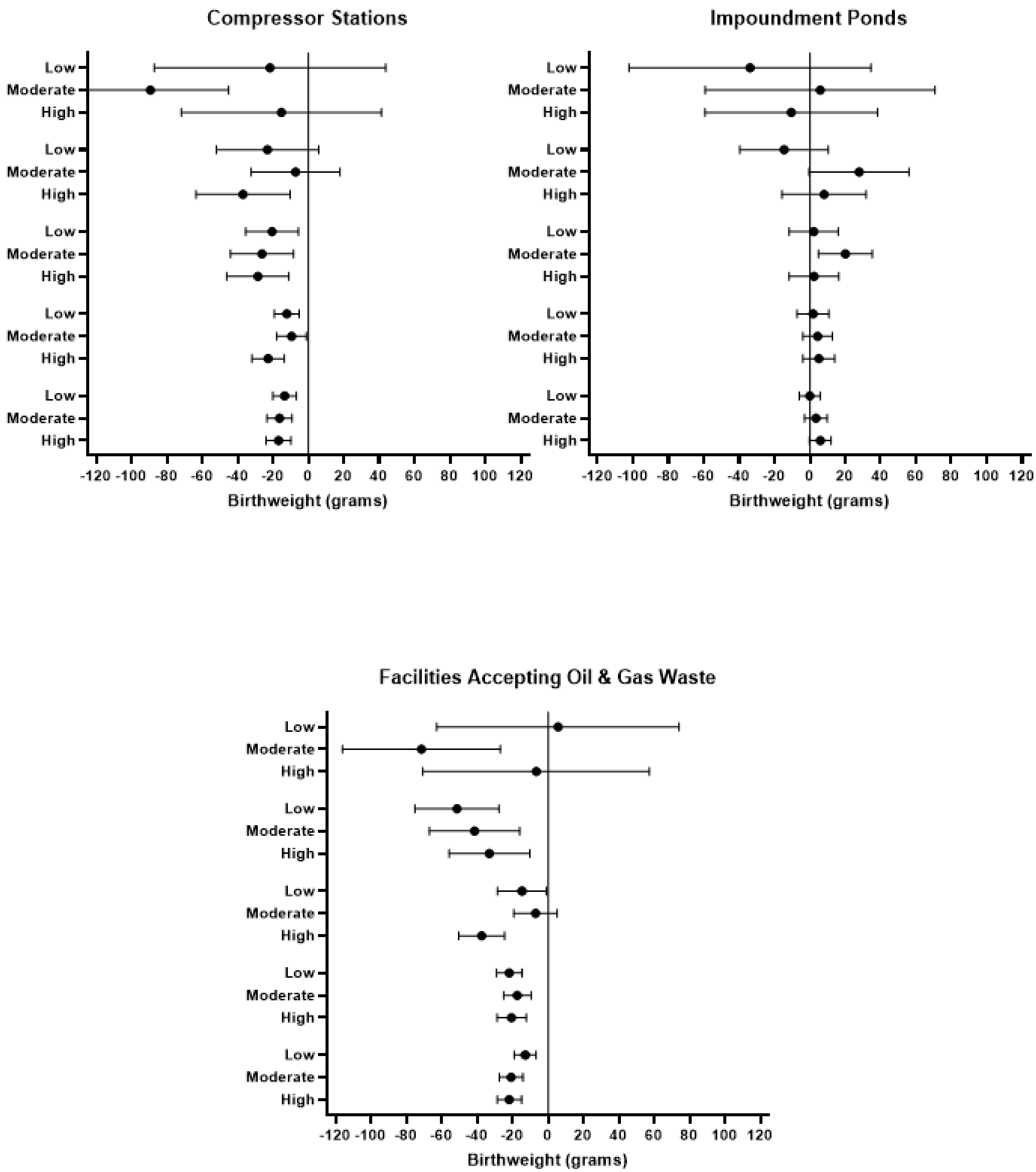


Figure 17. Forest Plots for Term Birthweight (grams) Non-Well Exposure Models

Exposure to PM2.5

As shown in Table 25 and in Figure 18, fine particulate matter, or PM 2.5 concentrations, have gradually declined over the course of the 2010-2018 period available for these data.

In December 2012, the EPA changed the primary annual fine particle standard from 15µg/m^3 to 12µg/m^3; areas are considered to meet this standard if their 3-year average annual PM 2.5 concentrations are equal to or less than 12µg/m^3 [38]. In 2010, both Allegheny and Westmoreland were above 12µg/m^3, but by the following year all counties were below that level and sustained it throughout the study period. It is likely that reductions in PM 2.5 pollution as shown by our data are due, in part, to the necessity of meeting this improved pollution standard. In 2021, the American Thoracic Society[39] recommend the standard for long-term exposure to PM2.5 be lowered to 8µg/m^3. County averages in 2016-2018 trend closer to this value; however, Allegheny County in 2018 was higher than 8µg/m^3. While the county averages are often below the 12µg/m^3 and close to the 8µg/m^3 benchmark in later years, geographic variability exists throughout each county, resulting in a significant portion of the population residing in areas below the respective benchmarks.

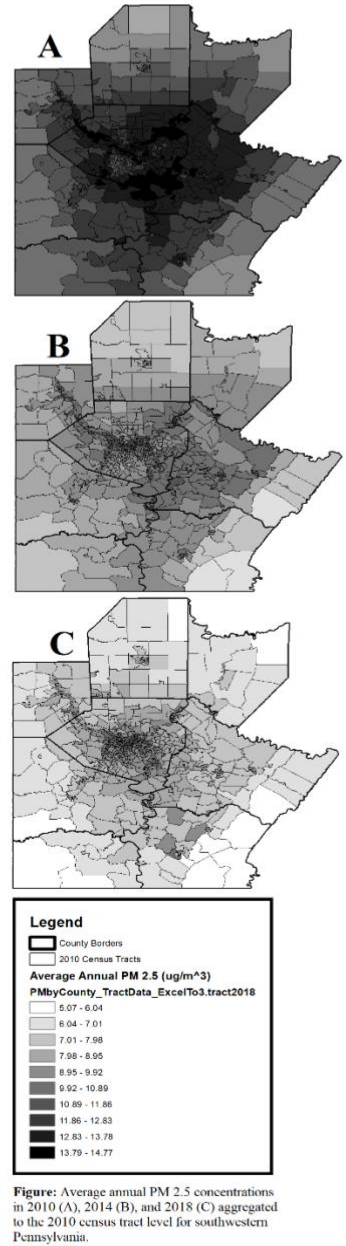


Figure 18. Study Area Maps of PM2.5 Values

Table 25. Average Annual PM2.5 (µg/m^3) by County for Study Region

County	2010	2011	2012	2013	2014	2015	2016	2017	2018
Allegheny	13.13	10.99	10.32	10.03	9.87	10.09	9.48	9.75	8.68
Armstrong	11.07	10.24	9.14	9.13	8.65	8.45	8.24	8.48	6.51
Beaver	11.24	10.15	8.93	9.72	9.00	8.91	8.39	8.42	7.23
Butler	10.39	9.63	8.40	8.86	8.09	8.13	7.79	8.33	6.82
Fayette	11.04	10.09	9.11	8.31	8.17	8.77	7.47	7.84	6.33
Greene	11.29	9.61	8.89	8.11	8.22	8.37	7.06	7.32	6.24
Washington	11.65	9.83	9.02	9.07	8.76	9.00	7.78	8.02	6.97
Westmoreland	12.17	10.88	9.94	9.52	9.25	9.30	8.65	8.92	7.23

Table 26 shows, for each of the three birth outcomes, the adjusted models for exposure to PM2.5 as a continuous term (no cut points were used) for the 153,339 births with PM2.5 measures. There was a statistically significantly elevated odds ratio for preterm birth (22-36 weeks gestation), indicating an increase in odds of preterm birth of 7% for each increase of 10μg/m^3 of PM2.5. We did not find evidence of increased risk with exposure to PM2.5 for either SGA or decreased term birthweight (37-41 weeks gestation).

Table 26. Association Between Exposure to PM2.5 (μg/m^3, continuous) and Birth Outcomes

Outcome	Adjusted OR[1] (95%CI) (per 10μg/m^3 PM2.5)
SGA	0.98 (0.97, 1.00)*
Preterm birth	1.07 (1.05, 1.10)*
Outcome	Adjusted Term Birthweight (grams)[1] (95%CI) (per 10μg/m^3 PM2.5)
Term birthweight (grams)	3.8 (2.0, 5.6)*

1- Models adjusted for county, neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, gestational diabetes, parity, smoking during pregnancy and three months prior, and SDI. Term birthweight model additionally adjusted for gestational age.

* $p<0.05$; ** $p<0.001$

PM2.5 was then dichotomized at 8μg/m^3, as recommended by the American Thoracic Society[39] and recently implemented by Goobie et al.[40], as shown in Table 28. PM2.5 was also split at 8μg/m^3 and 12μg/m^3.

Only 5% of our cohort with exposure to PM2.5 were exposed to levels at or below 8μg/m^3. The counties with lower PM2.5 had fewer births and exposure was an average of the year prior to birth, which reduced the number of births with PM2.5 exposure levels at or below 8μg/m^3.

In our cohort, 8,189 births had PM2.5 exposure at or below 8μg/m^3. Ten percent of births (n=15,840) had PM2.5 exposure greater than 12μg/m^3.

In the model using the >=8μg/m^3 cutoff, there was a statistically significant 8% increased risk of preterm birth compared to those below 8μg/m^3. In the model splitting exposure at 8μg/m^3 and 12μg/m^3, the odds ratios increased with increasing PM2.5 exposure, with those exposed to greater than 12μg/m^3 having a statistically significant 30% excess for preterm birth.

Table 27. Association Between Exposure to PM2.5 (μg/m^3, categorized) and Preterm Birth

PM2.5 (μg/m^3) Characterization	Adjusted OR[1] (95%CI)
Cutoff at >=8μg/m^3	
<8μg/m^3	--
>=8μg/m^3	1.11 (1.01, 1.23)*
Cutoffs at >=8μg/m^3 and >12μg/m^3	
<8μg/m^3	--
>=8 μg/m^3 and <=12μg/m^3	1.11 (1.00, 1.22)*
>12μg/m^3	1.30 (1.15, 1.46)**

1- Models adjusted for county, neonate sex, APNCU index, maternal age (centered at the mean), maternal race, maternal education level, maternal BMI, gestational diabetes, parity, smoking during pregnancy and three months prior, SDI

* $p<0.05$; ** $p<0.001$

Discussion

This population-based study of birth records from 2010-2020 in eight Southwestern Pennsylvania counties assessed associations between UNGD activity and three birth outcomes: small for gestational age, preterm birth (22-36 weeks gestation), and term (37-41 weeks gestation) birthweight. Similar to other studies on UNGD and birth outcomes, we found mixed results. To help frame the study conclusions, we are using the following classifying terms and criteria:

1. There are no data to suggest/support an increased risk:
   a. No statistically significantly elevated odds ratios
   b. Odds ratios at or near 1
   c. Odds ratios below 1 (with or without statistical significance)

2. There are limited data to suggest/support an increased risk:
   a. Statistically significantly elevated odds ratios in a low or moderate tertile
   b. Not statistically significant elevated odds ratios in multiple tertiles

3. There are moderate data to suggest/support an increased risk:
   a. Statistically significantly elevated odds ratios in multiple low or moderate tertiles
   b. Statistically significantly elevated odds ratios in a high tertile

4. There are strong data to suggest/support an increased risk:
   a. Statistically significantly elevated odds ratios in multiple tertiles
   b. Statistically significantly elevated odds ratios that increase across low, moderate, and high tertiles

For our primary exposure of interest, UNGD activity, our results are summarized below.

Small for gestational age (SGA): In this study, we found no data to support an increased risk of SGA and well phase activity in the well pad preparation, drilling, or hydraulic fracturing phases, nor with cumulative well count. There were consistently statistically significantly reduced odds ratios in the 10-mile buffer for well pad preparation. There were moderate to strong data to suggest an increased risk with the production phase. Odds ratios in the 2-, 5-, and 10-mile buffers were statistically significantly elevated 8-12%, with limited evidence of increasing risk with increasing intensity.

Preterm (22-36 weeks gestation): In this study, we found no data to support an increased risk of preterm birth and cumulative well count, nor with well phase activity in the well pad preparation, hydraulic fracturing, or production phases. There were statistically significantly reduced odds ratios for cumulative well count in all buffers and the trend test was statistically significant in the 10-mile buffer. Odds ratios for the production phase were statistically significantly reduced in the 5- and 10-mile buffers. There were limited data to suggest an increased risk with the drilling phase.

Term (37-41 weeks gestation) birthweight: In this study, we found no data to support an increased risk of term birthweight and well phase activity in the well pad preparation or hydraulic fracturing phases. Term birthweights in the 5- and 10-mile buffers were statistically significantly elevated. There were limited data to suggest an increased risk with the drilling phase, moderate data to suggest an increased risk with cumulative well count, and strong data to suggest an increased risk with the production phase, with statistically significant reductions in birthweight with increasing intensity of exposure.

Table 28 shows the results of the previous literature in comparison with this study (last row). Previous studies have had mixed results for these three outcomes, as shown. Our study replicated the methods of Casey et al.[6] in Northeastern PA and is also similar to the study performed by Whitworth et al.[10] in Texas. Stacy et al.[5], also with a focus in Southwestern Pennsylvania, identified an association between SGA and UNGD activity, as did Hill[26] and Tran[27]. Neither Casey et al[6] nor Whitworth et al[10] found a similar association. Casey et al. [6] and Whitworth et al.[10,12] both found statistically significant odds ratios in the third tertile (T3) of UNGD activity and preterm birth.

This study did not find statistically significant excesses for preterm birth in cumulative well count, a cumulative measure of UNGD activity or in the phase specific metrics with the exception of a limited association in the drilling phase. The association with preterm birth identified in Whitworth[10] was stronger than the association found here. The current study found a strong association between reduced term birthweight and the production phase, a moderate association with cumulative well count, and a limited association with the drilling phase. Casey et al[6] identified a not statistically significant 20 gram reduction with the highest quartile (Q4) of UNGD exposure and Whitworth et al.[41] found similar not statistically significant reduced birthweights. Stacy et al[5] found a statistically significant 21 gram reduction in birthweight associated with Q4 of inverse-distance weighted well count.

The varying exposure characterizations make direct comparisons difficult between many studies. Phase-specific analyses help pinpoint the timing and degree of risk associated with UNGD activity. One possible difference between this and other studies that could explain some of the mixed associations is that our cohort contains a significant number of births occurring in more recent times. If UNGD activities have changed over time to result in less environmental impact, then that could attenuate some of the effect sizes seen here relative to previous work.

Table 28. Summary of UNGD Model Results from Peer-Reviewed Literature and Current Study

Year	First Author	State	SGA	Preterm Birth	Term Birthweight
2014	McKenzie[23]	CO	--	N	N
2015	Stacy[5]	PA	Y Q[1]4 IDW well count OR[2]=1.34 (1.10, 1.63)	N	Y Q4 IDW well count BW[3] = -21 (-30, -12)
2016	Casey[6]	PA	N	Y Q4 UNGD OR=1.4 (1.0, 1.9)	N
2017	Currie[22]	PA	--	Y	Y BW = -39g
2017	Whitworth[10]	TX	N	Y T[4]3 UNGD 0.5-mile buffer OR= 1.14 (1.03, 1.25)	N

				2-mile buffer OR = 1.14 (1.07, 1.22) 10-mile buffer OR=1.15 (1.08, 1.22)	
2018	Hill[26]	PA	Y	N	Y
2018	Whitworth[12]	TX	--	Y T3 UNGD Drilling OR=1.20 (1.06, 1.37) Production OR=1.15 (1.05, 1.26)	--
2020	Cushing[28]	TX	--	Y Q4 well count OR=1.31 (1.14, 1.49)	Y Q4 well count BW=−19.4 (−36.7, −2.0)
2020	Gonzalez[17]	CA	--	N[5]	--
2020	Tran[29]	CA	Y[6] High vs no production OR=1.22 (1.02,1.45)	N	Y[6] High vs no production BW=−36g (−54, −17)
2021	Willis[18]	TX	N	--	Y 0-1 v 3-10km BW= –7.3g (–11.6, –3.0)
2022	Pitt SPH	PA	Moderate/strong Production phase	Limited Drilling phase	Limited Drilling phase Moderate Cumulative well count Strong Production phase

1– Q=quartile
2 – OR=odds ratio
3 – BW=birthweight
4 – T=tertile
5- Association only observed in very preterm births (<31 weeks)
6 – Association only observed in rural and not urban areas

Non-Well Exposures

We examined non-UNGD activity exposures as secondary sources in this study. Table 29 summarizes the findings between our birth outcomes and non-UNGD well phase exposures.

Table 29. Summary of Increased Risk of Adverse Birth Outcomes in Non-Well Exposure Model Results

Type of Exposure	SGA	Preterm birth	Term birthweight (grams)
Compressor stations	Limited	None	Moderate
Impoundment ponds	None	None	None
Facilities accepting oil and gas waste	Limited	None	Moderate
PM2.5 (µg/m^3)	None	Moderate	None

We found limited data to support an association for small for gestational age and proximity to facilities accepting oil and gas waste, particularly within 1 mile. Industrial air pollution has previously been shown to be associated with SGA, especially during the first two trimesters[42]. Maternal exposure to PM10 has also shown to be associated[43]. Future work should examine gestational exposure windows as well as the amount and type of waste accepted by the facilities.

There were moderate data to support that reductions in term birthweight were associated with proximity to both compressor stations and facilities accepting oil and gas waste. Previous studies have identified associations between birthweight and UNGD[5,18,22,26,28,29], but few have investigated UNGD infrastructure. These results indicate that non-well activities may also have impacts on birth outcomes. Additional studies should confirm and explore the relationship further.

We also found a moderate association between preterm birth and PM2.5. This association has been shown previously in multiple studies in the United States and internationally[46-49]. Liu et al[47] identified a statistically significant 4% excess for preterm birth with each 10 $\mu g/m^3$ increase in PM2.5 in the first and third trimesters, very similar to the 5% excess identified here. Future work with the PM2.5 data should also include sensitivity analyses evaluating other time windows of exposure, various lengths of exposure, constituent analysis, and other characterizations of the metric.

UNGD activities also have the potential to produce a variety of air pollutants, including PM2.5 to varying degrees. Beginning with the 2012 reporting year, the PA DEP has collected self-reported emissions data from the UNGD industry We noted these self-reported emissions for UNGD wells can vary several orders of magnitude between individual sites and over different years for the same site (http://cedatareporting.pa.gov/reports/powerbi/Public/DEP/AQ/PBI/Air_Emissions_Report). Our exposure metrics applied here essentially weight the behavior of all wells equally varying only be density and stage of activity, which does not allow discrimination of high emission wells from low emission wells. Thus, it is possible that a subset of wells with high polluting potential could negatively impact nearby residents, especially given the robust effect seen with region wide PM2.5 levels.

We evaluated multiple buffer distances in this study. A 2018 Delphi study evaluated setback distances for UNGD[14]. After three rounds of discussion with 18 panelists, consensus was reached that setbacks less than 0.25 mile should not be recommended and additional setbacks should be recommended for vulnerable groups. However, the panel did not reach consensus on setback distances between 0.25 and 2 miles. A review by Deziel et al.[16] of the association of UNGD and various health outcomes, including births, advocated for policy changes, including assessing setbacks. We found some evidence of associations for increased risk of small for gestational age during the well pad preparation and drilling phases and for preterm birth during the production phase at the smallest buffer, 0.5 miles. However, even with our population-based cohort of births, the small sample size led to wide confidence intervals. Future analyses of these results should include examining different functional forms of the exposure metric and considering the contaminants and exposures occurring during each phase.

Strengths and Limitations

This study had considerable strengths, including a very large population and assessing multiple characterizations of the exposure metrics at multiple buffer distances. These phase-by-buffer analyses provide new and important information about the associations of UNGD with our three birth outcomes. However, our analyses were proximity and density-based and not associated with any specific exposure or pathway. Future studies should include defined exposure pathways with the collection of biospecimens to help elucidate potential paths. Additionally, we did not evaluate heterogeneity in well conditions or techniques by operator. It is feasible that different conditions may exist by operator, well, or well pad leading to differing levels of exposure.

Epidemiologic studies address risk at the population level and not for any specific individual. Even in our large population-based cohort study, we had small sample sizes in some analyses, especially those within our smallest buffer distances and during shorter well activity phases (e.g., hydraulic fracturing). This included an inability to examine low Apgar score as an outcome, similar to Casey et al.[6] An analysis encompassing the entire state of PA, or several states, may be necessary to get an adequately powered study for this outcome. We used obstetric estimate of gestational age from the birth certificate. While research has shown excellent specificity, positive predictive value, and negative predictive value[50], it could introduce error when calculating preterm and small for gestational age statuses. The rates of SGA (9.2%) and preterm births (22-36 weeks, 7.4%) found in this study are slightly below the US averages of 10%[35] and 8.5% for singleton births[51], respectively. This could indicate better maternal and fetal care in our study area, although the rate of adequate and adequate plus prenatal care in this study (74.7%) is very similar to that in the US (77.6%)[51]. Additionally, we did not adjust for multiple comparisons. Some of the relationships between outcome and exposure may indicate evidence of a threshold effect, which was not assessed in the functional forms of the exposures examined here. Future studies should examine non-linear and other functional forms. There were some statistically significantly increased risks (both odds ratios and reduced birthweight) that lacked a "dose-response" relationship (i.e., risk did not increase with increasing intensity of exposure) often in terms of buffer zone and intensity metric. These could be due to small sample sizes in certain subgroups, to multiple comparisons or could be spurious. The trend test assessed the linear relationship of the exposure tertiles, and some trend tests were statistically significant even when odds ratios (or term birthweights) were close to the reference level. It may also be the case that, although we used as our comparison those residing greater than 10 miles from UNGD activity, there is no such thing as a truly non-exposed group given the large density of wells, and the relatively few births in the unexposed group. It may also be true that air pollution is acting as a confounder here, where the unexposed controls who were slightly more likely to reside in Allegheny County, were not impacted by fracking, but have higher levels of PM2.5. Future models should include PM2.5 measurements with UNGD activity.

In contrast to Casey et al.[6] which included births from 2009 to 2013, we examined 11 years of birth data and corresponding UNGD activity data during a period of high activity in Southwestern PA (2010-2020). We anticipate that technological changes may have occurred over that time that may modify the associations with UNGD in more recent years.

Our results provide important new information about the associations between UNGD activity and birth outcomes, but also provide direction for future analyses. The findings related to oil and gas infrastructure need to be examined in more detail, particularly the types and amounts of waste accepted by such facilities. Moreover, additional work is needed to ascertain why the production phase seems to pose the most risk for reduced term birthweight, and to a lesser extent, SGA. The similar associations related to the production phase among term birthweight and SGA, both outcomes related to in utero growth, lend support to the consistency of those findings. Of the previous studies which examined both SGA and term birthweight, Stacy[5] and Tran[27] also identified associations with UNGD activity and both outcomes. Hill[26] found an association with SGA but not term birthweight; Willis[18] found an association with term birthweight but not SGA, and Casey[6] and Whitworth[10] did not find associations with either outcome.

While we focused here on term birthweight and preterm birth 22-36 weeks, those infants born preterm with low birthweight or preterm prior to 31 weeks may be especially vulnerable and those associations should be examined. Finally, the exposures associated with UNGD are complex and multi-faceted. As recently advocated by Deziel et al.[19], future work should include multiple exposures and identify ways in which exposure pathways can be delineated.

Appendix

Table 1. Peer-Reviewed Literature on Birth Outcomes and Associations with UNGD

Year	First Author	Journal	Geographic Area	Population	Distance (miles/km)	Metric (e.g., IDW, CWD)	Data Source (e.g., DEP, self-report,)	Findings
2014	McKenzie	Environmental Health Perspectives	CO – restricted to rural areas and towns with pops < 50,000 in 57 counties	Singleton live births from 1996 through 2009, excluding non-white births due to low %	10 mi radius of maternal residence	IDW natural gas well counts (tertiles; referent group = 0 wells w/i 10 mi)	Colorado Oil and Gas Information System (COGIS)	Association between density and proximity of natural gas wells within a 10-mile radius of maternal residence and prevalence of CHDs
2015	Casey	Epidemiology	PA	Singleton births delivered at Geisinger, 2006-2013 (but then excluded births < 2009)	N/A – used all wells in the state	ID^2W, incorporating four phases of well development (quartiles)	PA DEP, PA DCNR, SkyTruth	Association between UNGD activity and preterm birth that increased across quartiles, 4^{th} q OR=1.4
2015	Stacy	PLoS ONE	PA -- Butler, Washington, and Westmoreland counties	Singleton births in the study counties from 2007-2010	10 mi radius of maternal residence and within the study counties	IDW well count (quartiles); Used active unconventional gas drilling wells from 2007-2010	PA DEP	Lower birth weight (21 g) and higher incidence of SGA (4.8% vs 6.5%) comparing most to least exposed
2016	Ma	Journal of Epidemiology and Public Health Reviews	PA	Singleton live births from 2003-2012	N/A – zip-code level	Well density = total number of unconventional wells	PA DEP	UNGD was not associated with birth defects prevalence rate

						per sq km for each zip-code		trend and level changes
2017	Currie	Science Advances	PA	Singleton births in the state from 2004-2013; Subset of births to mothers residing w/I 15 km of a well site	0-1 km, 1-2 km, 2-3 km, …, 10-15 km (with 0-1, 1-2, 2-3 km distance bands being defined as "near"; 3-15 km as "far")	Binary variable indicating if there is at least one well within the specified radius of the mother's residence; Used all oil and gas wells marked as unconventional and not currently plugged at time of study (i.e., active)	PA DEP Internal Operator Well Inventory	Greater incidence of low birthweight and lower birthweight within 1 km and 3km; little evidence for health effects at distances beyond 3 km
2017	Whitworth	PLoS ONE	TX – 24-county Barnett Shale area	Singleton births and fetal deaths from 11/30/2010-11/29/2012	0.5, 2, and 10 mi radius of maternal residence	ID^2W well count (tertiles; referent group = women with at least 1 well > 10 km but < 20 km of residence)	DrillingInfo	Increased adjusted odds of preterm birth in highest tertiles of the ½-, 2-, and 10-mile metrics. Little indication of association with SGA or term birthweight.
2017	Busby	Journal of Environmental Protection	PA	Live births and infant deaths (0-28 days, 0-1 year), 2003-2010	N/A -- county level	Comparison of time period before (2003-2006) and after fracking expansion (2007-2010); violations per birth; water wells per birth	PA DEP (fracking wells, violations), PA DCNR (drilled water wells)	Fracking associated with early infant mortality
2018	Hill	Journal of Health Economics	PA	Births from 2003-2010	2.5 km of maternal residence (also tested radii of 2, 3, 3.5, 4, 4.5, 5 km)	Binary variable indicating presence of any gas wells w/i specified radius;	PA DEP (also including permit data)	Associated with reduced average birth weight among infants born to mothers

						CWD of gas wells w/i specified radius		living within a 2.5 km
2018	Whitworth	Environmental Health Perspectives	TX – 24-county Barnett Shale area	Singleton births from 11/30/2010-11/29/2012	0.5 mi of maternal residence	ID^2W count of wells in the drilling phase (tertiles; referent group = 0 wells w/i 0.5 mi); ID2W sum of cumulative daily gas production volume (MCF) among wells in the production phase (tertiles; referent group = 0 wells w/i 0.5 mi)	DrillingInfo	Evidence of differences in phase- and trimester-specific associations of UNGD and preterm birth and indication of particular risk associated with extremely preterm birth
2019	Apergis	Environmental Science and Pollution Research	OK	Births from 2006-2017	0-1, 1-5, 5-10, and 10-20 km of maternal residence	CWD (number of wells within buffer)	Oklahoma Corporation Commission Oil and Gas Division	Unidirectional causal relationship between fracking and infant’s health
2019	Casey	Environmental Research	PA	Singleton births delivered at Geisinger to women w/ and w/o depression or anxiety, 2009-2013	N/A – used all wells in the state	ID^2W, incorporating four phases of well development (quartiles)	PA DEP, PA DCNR, SkyTruth	Increased antenatal anxiety or depression in mothers in highest quartile of UNGD activity
2019	Janitz	Environment International	OK	Singleton births from 1997-2009	2 mi of maternal residence (also tested radii of 5 and 10 mi)	ID^2W well count (tertiles); IDW well count (tertiles)	Oklahoma Corporation Commission	Increased prevalence of neural tube defects among children with

								natural gas activity compared to no wells)
2019	McKenzie	Environment International	CO -- restricted to 34 counties with 20 or more active wells (areas with intense oil and gas activity)	All non-chromosomal congenital heart defect (CHD) cases and randomly selected singleton live birth controls, 2005-2011	10 mi radius of maternal residence	IDW well count; intensity adjusted IDW well count (IA-IDW) incorporating relative intensity of air pollution sources not associated with oil and gas activities	Colorado Oil and Gas Information System; EPA TRI; US Geological Survey (mines), Colorado Department of Public Health	CHDs more likely in medium and high intensity exposure groups
2020	Cushing	Environmental Health Perspectives	TX -- rural areas of the 27 counties comprising the Eagle Ford Shale	Singleton births from 2012-2015	5 km of maternal residence	CWD (number of wells within 5 km of maternal residence categorized as none, low, med, high); Number of individual nightly flaring events (median split); Total flared area (median split); ID2W sum of flares (median split)	DrillingInfo; VIIRS	Exposure to a high number of nightly flare events was associated with 50% higher odds of preterm birth and shorter gestation compared with no exposure. Women exposed to a high number of wells vs. no wells within 5km had a higher odds of preterm birth shorter gestation and lower average birthweight

2020	Gonzalez	Environmental Epidemiology	CA – 8 counties comprising San Joaquin valley region	Singleton births from 1998 to 2011 delivered at nonmilitary hospitals in the study region	10 km radius of maternal residence	ID^2W well count (tertiles)	California Geologic Energy Management Division (CalGEM; formerly DOGGR), Enverus (private data aggregation service)	Increased ORs for preterm birth with high exposure to wells in the first and second trimesters for births delivered at ≤31 weeks, confined to births to Hispanic and non-Hispanic Black women and to women with ≤12 years of educational attainment
2020	Tran	Environmental Health Perspectives	CA -- Sacramento Valley, San Joaquin Valley, South Central Coast, and South Coast air basins (where well densities were highest)	Singleton births from 2006-2015 to mothers living w/i 10 km of a well	1 km of maternal residence	Total oil and gas production volume among active wells (categorized as none, moderate, high); CWD for inactive wells (categorized as none, low, mod, high)	CA Division of Oil, Gas, and Geothermal Resources	Associations found with low birthweight, SGA, and decreased term birthweight in rural areas
2021	Willis	Environmental Health Perspectives	TX	Singleton births from 1996-2009 to mothers living w/i 10 km of a well	Exposed w/i 3 km; Unexposed 3-10km	Binary exposure to well within buffer on day of birth	TX Dept of Vital Stats; Enverus Drilling Info	Small reduction in term birthweight; no association with SGA

IDW: Inverse distance weighting

CWD: Cumulative well density

Table 2. Zip codes excluded from the City of Pittsburgh

Zip code	All or part City of Pittsburgh
15106	Part City
15120	Part City
15201	All City
15203	All City
15204	Part City
15205	Part City
15206	All City
15207	All City
15208	All City
15210	Part City
15211	All City
15212	Part City
15213	All City
15214	Part City
15215	Part City
15216	Part City
15217	All City
15218	Part City
15219	All City
15220	Part City
15221	Part City
15222	All City
15224	All City
15226	Part City
15227	Part City
15230	All City
15232	All City
15233	All City
15234	Part City
15235	Part City
15240	Part City
15260	All City
15282	All City

Table 3. Body Mass Index (BMI) calculation and cutoff values

For births to mothers aged 20 years or younger, we used the following criteria based on the CDC's recommended youth BMI-for-age cutoffs:
• **Underweight:** <5th percentile
• **Normal:** 5th to <85th percentile
• **Overweight:** 85th to <95th percentile
• **Obese:** ≥ 95th percentile
• Unknown: missing height and/or weight
For births to mothers aged 21 years or older, or for births for which maternal age was missing, we used the following criteria based on the CDC's recommended cutoffs for adults:
• **Underweight:** BMI <18.5
• **Normal:** BMI ∈ [18.5, 25)
• **Overweight:** BMI ∈ [25, 30)
• **Obese:** BMI ≥ 30
• Unknown: missing height and/or weight

Table 4. Calculation of Community Socioeconomic Deprivation Index

An index of socioeconomic deprivation incorporating six indicators from the 2015-2019 American Community Survey 5-year estimates from the US Census:
• Percent less than high school education
• Percent in poverty
• Percent not in the labor force
• Percent on public assistance
• Percent does not own a vehicle
• Percent civilian unemployment
The six indicators were standardized for direction, natural log-transformed, if necessary, z-scored using the standard deviations for Pennsylvania, and summed to create the final, unitless index for each county, township, or census tract. The total number of communities was divided into quartiles of socioeconomic deprivation index. Higher values of the index reflect greater community socioeconomic deprivation.

Table 5. Additional environmental exposure data sources considered for inclusion

Category	Description	Time period	Data source
Other oil and gas-related activity	Impoundment ponds	2005-2017	SkyTruth
	Oil and gas waste facilities	2000-2020	Pennsylvania Department of Environmental Protection (PA DEP)
	Underground injection disposal wells	2000-2021	United States Environmental Protection Agency (US EPA)
	Compressor stations	2000-2019	PA DEP
	Gas well and compressor station air emissions	2012-2019	PA DEP

	Hydraulic fracturing chemical disclosure registry	2008-2021	FracFocus
	Conventional wells	1985-2020	PA DEP
Other industries	Toxic Release Inventory (TRI) sites	1990-2019	US EPA
	Superfund/National Priorities List (NPL) sites	1985-2021	US EPA
Air quality	National Air Toxics Assessment (NATA)	1996, 1999, 2002, 2005, 2011, 2014	US EPA
	Ambient monitoring air pollution data	2000-2021	US EPA, PA DEP
	Satellite imagery-based air pollution data	2000-2018	Dalhousie University
Water quality	National Pollutant Discharge Elimination System (NPDES) and Water Quality Management (WQM) permitted wastewater facilities	1985-2021	PA DEP
	Electronic Discharge Monitoring Report (eDMR)	2007-2020	PA DEP
	Safe Drinking Water Act standards	2020	PA DEP
	Clean Water Act standards	2021	US EPA
	Safe Drinking Water Information System (SDWIS)	1985-2021	US EPA
	Water Quality Portal (WQP)	1985-2020	US EPA & United States Geological Survey (USGS)
	Assessment and Total Maximum Daily Load Tracking and Implementation System (ATTAINS)	2002-2015	US EPA

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ATTACHMENT C

STUDY 3

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Unconventional natural gas development and birth outcomes in Pennsylvania, USA

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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

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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.

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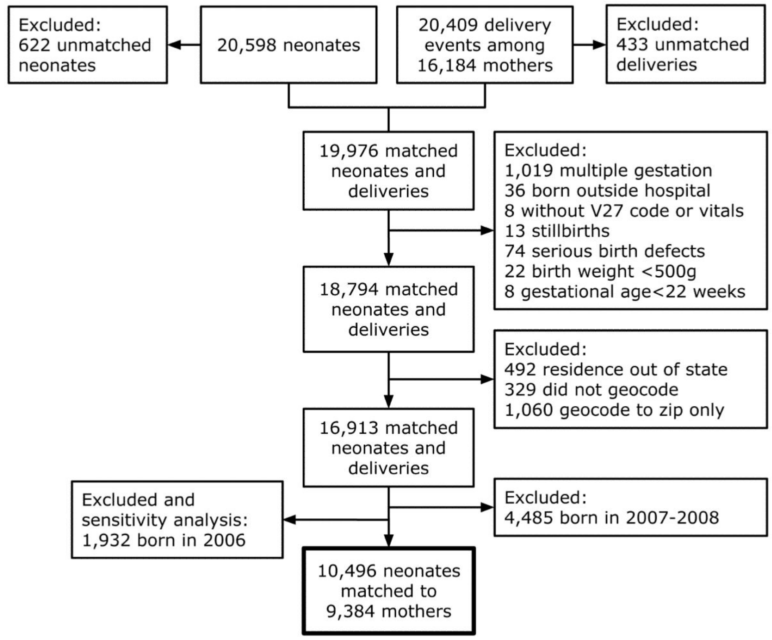

Figure 1.

Flow diagram of study population assembly

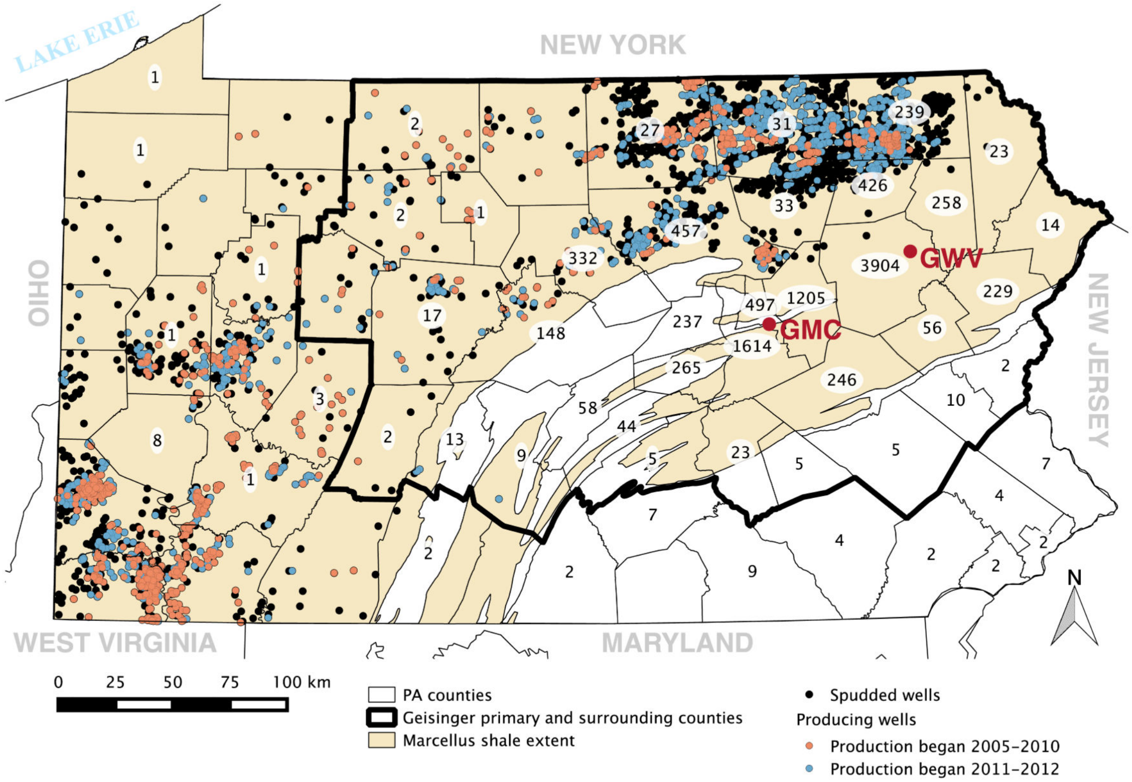

Figure 2.

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.

ATTACHMENT C

STUDY 4

A Section 508–conformant HTML version of this article
is available at https://doi.org/10.1289/EHP11092.

Unconventional Oil and Gas Development Exposure and Risk of Childhood Acute Lymphoblastic Leukemia: A Case–Control Study in Pennsylvania, 2009–2017

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Background: Unconventional oil and gas development (UOGD) releases chemicals that have been linked to cancer and childhood leukemia. Studies of UOGD exposure and childhood leukemia are extremely limited.

Objective: The objective of this study was to evaluate potential associations between residential proximity to UOGD and risk of acute lymphoblastic leukemia (ALL), the most common form of childhood leukemia, in a large regional sample using UOGD-specific metrics, including a novel metric to represent the water pathway.

Methods: We conducted a registry-based case–control study of 405 children ages 2–7 y diagnosed with ALL in Pennsylvania between 2009–2017, and 2,080 controls matched on birth year. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between residential proximity to UOGD (including a new water pathway-specific proximity metric) and ALL in two exposure windows: a primary window (3 months preconception to 1 y prior to diagnosis/reference date) and a perinatal window (preconception to birth).

Results: Children with at least one UOG well within 2 km of their birth residence during the primary window had 1.98 times the odds of developing ALL in comparison with those with no UOG wells [95% confidence interval (CI): 1.06, 3.69]. Children with at least one vs. no UOG wells within 2 km during the perinatal window had 2.80 times the odds of developing ALL (95% CI: 1.11, 7.05). These relationships were slightly attenuated after adjusting for maternal race and socio-economic status [odds ratio (OR) = 1.74 (95% CI: 0.93, 3.27) and OR = 2.35 (95% CI: 0.93, 5.95)], respectively). The ORs produced by models using the water pathway-specific metric were similar in magnitude to the aggregate metric.

Discussion: Our study including a novel UOGD metric found UOGD to be a risk factor for childhood ALL. This work adds to mounting evidence of UOGD's impacts on children's health, providing additional support for limiting UOGD near residences. https://doi.org/10.1289/EHP11092

Introduction

Childhood acute lymphoblastic leukemia (ALL) is a hematological malignancy that arises from immature B- and less commonly T-lymphoid immune cells.[1] ALL is the most common type of cancer in children (age 0–14 y), representing nearly 80% of childhood leukemia cases and 20%–30% of all childhood cancer cases.[1–3] Incidence of ALL typically peaks in children age 2–4 y,[1,4] indicating that the early life environment is likely etiologically important. Although long-term survival rates exceed 90%,[5] survivors may face health and wellness difficulties later in life, such as chronic illnesses (e.g., cognitive dysfunction, heart disease),[6–9] psychological issues (e.g., depression, anxiety),[9–11] and elevated risk of second primary cancers.[8] Despite a decrease in the incidence of cancer overall in the United States, the incidence of childhood ALL has continued to increase, underscoring the importance of primary prevention.

The etiology of ALL is likely multifactorial and attributable to both environmental exposures and underlying genetic susceptibility. Current evidence suggests that for most cases, ALL develops due to multiple genetic insults, such as chromosomal translocations or alterations.[12–14] The development of preleukemic clone cells commonly occurs after an initiating genetic insult from a chromosomal translocation *in utero*, with an additional genetic insult required for overt ALL to manifest.[2,4,14,15] Although the genetic and molecular processes behind the disease have been delineated, the upstream etiological agents triggering such biological insults remain poorly understood. Current evidence and the early age of peak ALL incidence suggest that exposure to environmental chemicals—particularly to chemicals that are hematotoxic, damage DNA, or interfere with the immune system—may provide a mechanism for pre- or postnatal insults.[2,16] To date, ALL has been linked to several environmental and chemical exposures, including ionizing or diagnostic radiation,[17,18] radon,[19] air pollution,[20–24] pesticides,[25–29] polybrominated diphenyl ethers,[30] and benzene.[22,31–35]

Unconventional oil and gas development (UOGD), commonly referred to as hydraulic fracturing or "fracking," is a complex process with the potential for releases of chemical and radiological contaminants into both water and air.[36] UOGD is a rapidly expanding source of energy and petrochemical production in the United States. Hydraulic fracturing, an important step in the UOGD process, involves pressurized injections of millions of gallons of water, chemicals, and proppant (e.g., sand) into underground rock formations to create small fissures, allowing natural gas to flow to the surface.[37] In addition to the natural gas, the injected fluids and formation water also rise to the surface as wastewater. A single well has been estimated to produce between 1.7 and 14 million liters of wastewater over the first 5 to 10 y of production, and this varies widely by producing formation.[38,39] The transport and storage of this wastewater may result in surface spills,[40–43] and improper management or structural failures of injection wells used for storage can result in migration of chemicals into groundwater or surface water.[44–46] Average annual spill rates (number of spills/UOG wells drilled) across four states was estimated at 5.6%, with 31.1% of wells ever reporting a spill; many spills occurred in watersheds serving as drinking water sources.[42]

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Hundreds of chemicals have been reportedly used in UOGD injection water or detected in wastewater, some of which have been associated with leukemia.[47] Known and suspected carcinogens include heavy metals, radioactive material, volatile organic compounds (e.g., benzene), and polycyclic aromatic hydrocarbons.[48,49] In addition to water pollution, UOGD has the potential to generate air pollution during well and road construction and through vehicle emissions from the transport of oil, gas, and wastewater.[50,51] Studies of UOGD-related air emissions have measured several carcinogens, including radioactivity, particulate matter (PM), and volatile organic compounds (e.g., benzene).[52–55] Furthermore, elevated levels of indoor radon were measured in homes near UOGD activity.[56,57] Additionally, the process of extracting natural gas also brings technologically enhanced naturally occurring radioactive compounds to the surface with ancient brine formation water, and drill cuttings and sludge from equipment may also contain radioactivity.[58,59] The potential for children living near UOGD to be exposed to chemical carcinogens and radiological contaminants is a major public health concern.

Research on the potential association between exposure to UOGD and risk of childhood cancer is urgently needed. To our knowledge, there have been only two published studies of this relationship to date. The first was an ecological study conducted in the state of Pennsylvania,[60] which compared standardized incidence ratios of childhood cancer before and after drilling and observed no difference; this analysis did not account for a latency period or adjust for confounders.[61] The second, a registry-based case–case study in Colorado, found that children and young adults with ALL (ages 0–24 y; $n = 87$ cases) were four times more likely to live in areas of greater oil and gas activity (conventional and unconventional combined) than controls, which were children with nonhematological cancers, based on models adjusted for multiple confounders.[62] The case–case methodology may have attenuated the true association if UOGD was a shared risk factor. The paucity of data on the association between UOGD and childhood cancer outcomes has fueled public concerns about possible cancer clusters in heavily drilled regions and calls for more research and government action.[63]

To advance understanding of the relationship between UOGD exposure and ALL risk and inform public policy, we conducted a registry- and population-based case-control study. This work builds on prior studies by incorporating a larger sample size, the use of cancer-free controls identified from birth records, and the use of UOGD-specific metrics, including a novel metric developed for capturing exposures through the water pathway.[64,65]

Methods

Study Setting, Population, and Design

We conducted a population-based case–control study in the commonwealth of Pennsylvania because it is home to intense oil and gas activity. More than 10,000 UOG wells were drilled in Pennsylvania between 2002 and 2017, with the place of drilling increasing sharply from 2007 to 2011.[66] In addition, more than 1,000 spills, 5,000 violations, and 4,000 resident complaints related to oil and gas were documented between 2005 and 2014 in Pennsylvania.[42,67] Further, up to one-third of domestic groundwater wells in Pennsylvania are located within 2 km of a hydraulically fractured well.[68]

Cases included all children diagnosed with ALL between the ages of 2–7 y in Pennsylvania from 2009 to 2017 (Figure 1). We chose this age range to cover the peak age of ALL incidence in

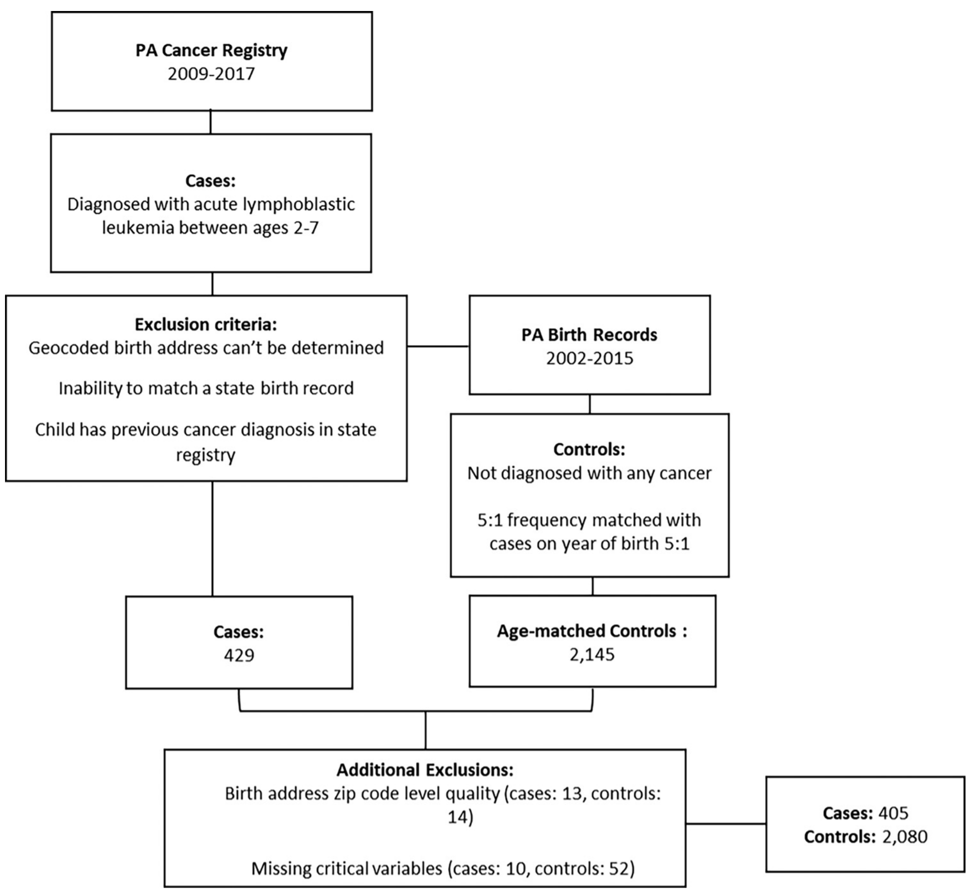

Figure 1. Data sources and selection process for Pennsylvania cases and controls (2009–2017).

the United States[69] and exclude cases of the etiologically distinct infant leukemia (diagnosis between the ages of 0–1 y).[70,71] We selected the years of diagnosis to ensure there was opportunity for exposure after drilling commenced in the state and a latency period of at least 1 y to account for the development of disease.[72] ALL cases ($n = 429$) were identified from the Pennsylvania state cancer registry by Pennsylvania Department of Health staff using ICD-O-3 sites C420, C421, C424 and Histology codes 9811–9818, 9826, and 9835–9837. Cases were then linked to their birth records available from the Pennsylvania Vital Records maintained by the Bureau of Health Statistics and Registries. Cases were excluded if *a*) the state could not match a birth record in Pennsylvania, *b*) the child had a previous diagnosis of cancer in the state cancer registry, and *c*) a birth address could not be obtained/geocoded beyond ZIP code level.

For each case, five control children were randomly selected by Pennsylvania Department of Health staff from live births in the Pennsylvania birth records with frequency-matching on birth year ($n = 2{,}145$; Figure 1). Reasons for excluding controls included: *a*) birth address could not be obtained or geocoded to street level, *b*) the child had a previous diagnosis of cancer in the state cancer registry, and *c*) the child was a sibling of a case or another control. After obtaining the data set, we performed additional geocoding [using SAS (version 9.4; SAS Institute Inc.] and checked geocode quality for both case and control children, excluding those whose birth address was not street-level quality or better ($n = 14$ cases; $n = 13$ controls). Because the missingness rate for several key covariates was very low, we elected to conduct a complete case analysis by excluding children from the study population missing the following covariates (established or suspected risk factors)[16,73–75]: maternal participation in the U.S. Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC, an individual-level representation of socioeconomic status), birth weight, and mode of delivery (Figure 1; $n = 10$ cases; $n = 52$ controls). We included 405 cases and 2,080 controls in our final analyses. The study protocol was approved by the institutional review board of Yale University (HIC #2000021809) and by the Pennsylvania Department of Health.

Exposure Assessment

We obtained and merged permit and production report data sets from the Pennsylvania Department of Environmental Protection's Office of Oil and Gas Management[66] to construct a data set of location, permit, and production data for UOG wells that were active (i.e., drilled or producing, as confirmed by having a reported spud date or a submitted production report) in Pennsylvania during the period 2001–2015. The data were then cleaned, and their quality were checked. For example, missing data on spud date, well type, and producing formation in the permit data sets were cross-referenced with and supplemented by the production data sets. Duplicate entries were addressed by preferentially retaining the most recent entry. Wells with a missing spud date were assigned a spud date equal to the first date of the earliest production report minus the median number of days between spud and first production in the data set. The final database included 9,578 active coalbed methane, gas, oil, and combined oil and gas wells in unconventional formations.

Maternal residential address at birth was obtained and geocoded from birth records for both cases and controls, and address at diagnosis was obtained from cancer registries for cases. Birth address was used to assign exposures using inverse distance-squared weighted (ID^2W) well counts (represented by $\sum_{i=1}^{n} \frac{1}{d_i^2}$ for all UOG wells within a buffer zone, where d is distance between the i^{th} UOG well and a residence), referred to as the "aggregate metric." We calculated this metric with buffer sizes of 2, 5, and 10 km. We selected two etiologically important exposure windows: *a*) 3 months prior to conception to 1 y prior to diagnosis, called the "primary window," and *b*) 3 months prior to conception to birth, called the "perinatal window." For the primary window, age-matched controls were assigned a reference date corresponding to the diagnosis date of a case. For the perinatal window, exposures were assigned using the respective birth dates of the cases and controls.

To capture water as a route of exposure to UOGD, we also calculated a flow-direction metric based on land-surface topography, inverse distance metric ID_{ups}, referred to as the "water pathway-specific metric." ID_{ups} is based on the widely accepted conceptual model that groundwater flow in regions of hill-and-valley topography occurs in the downhill direction, parallel to the topographic gradient.[76] ID_{ups} is represented by the equation $\frac{1}{u}$, where (u) is distance to the nearest upgradient UOG well, determined with the D-infinity algorithm in TauDEM. This metric and its underlying programming code was introduced by Soriano et al. and was subsequently applied in a study of UOGD-related drinking water exposure.[65] This exposure metric assumes that UOG wells that are located upgradient of a residence contribute more to exposure than downgradient wells, presuming that consumption or contact with groundwater from domestic wells is a major exposure source. The metric was calculated using buffer sizes of 2, 5, and 10 km around the maternal residence. Our selection of buffer sizes was informed by the hydrological (2 km) and epidemiological (5 and 10 km) literature,[64,65,76,77–81] and facilitates comparison between the aggregate metric and the water pathway-specific metric and comparisons with previous epidemiologic studies. We conducted a subanalysis using this metric as the main UOGD exposure assessment variable.

Residential Mobility

Residential mobility among pregnant women or in early childhood could introduce exposure misclassification.[82–85] We used three analyses to address the potential exposure misclassification introduced by residential mobility among pregnant mothers. First, we compared all case addresses at birth and diagnosis and assessed the distance moved as well as variables associated with mobility (e.g., socioeconomic status). Second, we examined the difference in cases' exposure classification at the birth and diagnosis addresses. Third, our selection of the perinatal exposure window, which restricts the window of exposure to 3 months prior to conception to birth, addresses mobility. The exposure estimate based on birth address is likely to be most accurate during this shorter time window (i.e., less opportunity to move residences), and pregnancy is an important etiological window for childhood leukemia.[14,15,29] We used the findings from these three analyses to provide context and aid interpretation of our results.

Covariates and Confounders

To account for potential confounding, we considered adjustment for both individual-level and area-level factors. We generated a list of *a priori* potential confounders informed by the literature that were available from birth records or publicly available data sources including sex, mode of delivery, birth weight, race, ethnicity, maternal education, air pollution exposure, and pesticide exposure.[2,20,21,25,33,73–75,86–88]

We estimated exposure to maternal and childhood residential air pollution using the U.S. Environmental Protection Agency (U.S. EPA) Bayesian space–time downscaler models, which provide daily estimates of average fine PM with an aerodynamic diameter

≤2.5 μm ($PM_{2.5}$) at census tract centroids.[89] We took the mean of daily average $PM_{2.5}$ measurements from 3 months prior to conception to 1 y prior to diagnosis to produce one representative $PM_{2.5}$ measurement for each individual. To represent maternal and childhood residential exposure to agricultural pesticides, we retrieved raster data of cropland for Pennsylvania from the U.S. Department of Agriculture National Agricultural Statistics Service CropScape.[90] Individuals were matched to the cropland map from their birth year, except for 2003 and 2004, which used a 2002 map, and 2005–2008, which used a 2008 map, due to data availability. We calculated the percent of land designated as cropland within buffers of 500 m and 1,000 m around each home (modeled after Reynolds et al.[91] and referred to this as "percent cropland").

We obtained information on community-level demographic and socioeconomic characteristics from the U.S. 2000 and 2010 Decennial Census [e.g., median household income, educational attainment, percentage of households living in poverty, housing occupancy, housing type (e.g., rented vs. owned)] for all Pennsylvania census tracts.[92] We also linked individuals to the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry Social Vulnerability Index (SVI), a composite metric representing 15 different social conditions, including socioeconomic status, demographics, and access to transportation, among other factors.[93]

Statistical Analyses

All statistical analyses were conducted in SAS (version 9.4; SAS Institute Inc.), and all tests were two-sided with an alpha level of 0.05. We used unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between UOGD exposure and ALL risk, adjusting for year of birth (i.e., the matching variable). We constructed separate models for each metric, for buffer size, and for both the primary

Table 1. Distribution of Pennsylvania study population characteristics (2009–2017).

	Cases ($n = 405$)	Controls ($n = 2080$)	
Variable	n (%)	n (%)	χ^2 p-value
Sex	—	—	0.57
Male	222 (55)	1,108 (53)	—
Female	183 (45)	972 (47)	—
Gestational age (wk)	—	—	0.76
<32 wk (Very preterm)	5 (1)	40 (2)	—
32 to <37 (Preterm)	35 (9)	162 (8)	—
37 to <39 (Early term)	78 (19)	436 (21)	—
39–41 (Term)	258 (64)	1,275 (61)	—
42+ (Postterm)	28 (7)	155 (7)	—
Out of limit, missing, no physician estimate	1 (1)	12 (1)	—
Birth weight	—	—	0.41
Low birth weight (<2,499 g)	27 (7)	172 (8)	—
Normal birth weight (2,500–3,999 g)	333 (82)	1,707 (82)	—
High birth weight (>4,000 g)	45 (11)	201 (10)	—
Delivery route	—	—	0.40
Vaginal	281 (69)	1,399 (67)	—
Cesarean	124 (31)	681 (33)	—
Mother's race	—	—	<0.0001
White	327 (81)	1,520 (73)	—
Black	29 (7)	333 (16)	—
Other	42 (10)	179 (9)	—
Not reported	7 (2)	48 (2)	—
Mother's ethnicity	—	—	0.90
Not Hispanic	370 (91)	1,888 (91)	—
Hispanic	31 (8)	173 (8)	—
Unknown	4 (1)	19 (1)	—
Mother's educational attainment	—	—	0.96
High school or less	54 (13)	266 (13)	—
Some college	221 (55)	1,129 (54)	—
Bachelor's	84 (21)	430 (21)	—
>16 y	46 (11)	255 (12)	—
Mother uses WIC	—	—	0.18
Yes	160 (40)	749 (36)	—
No	245 (60)	1,331 (64)	—
Median household income ($USD)	—	—	0.88
<$26,500	96 (24)	517 (25)	—
$26,500–$53,000	191 (47)	971 (47)	—
>$53,000	118 (29)	492 (28)	—
	Mean (SD)	Mean (SD)	—
Percent cropland (500 m[a])	—	—	0.24[b]
	13.8 (20.9)	12.5 (20.4)	—
	—	—	0.71[b]
CDC SVI percentile	54.0 (27.9)	53.4 (29.7)	—
Annual $PM_{2.5}$ (μg/m^3)	—	—	—
Primary window	11.7 (1.7)	11.7 (1.7)	0.93[b]
Perinatal window	12.4 (2.1)	12.4 (2.2)	0.91[b]

Note: Data are complete for all variables. p-Values generated using χ^2 tests. —, no data; CDC, U.S. Centers for Disease Control and Prevention; IQR, interquartile range; SVI, CDC/Agency for Toxic Substances and Disease Registry Social Vulnerability Index; USD, United States dollars; WIC, Supplemental Nutritional Program for Women, Infants, and Children.
[a]Used as a proxy for pesticide exposure, accounting for likely extent of pesticide drift; calculated for year of birth only.
[b]t-test p-value.

and perinatal exposure windows. We constructed two model types: minimally adjusted (i.e., only adjusting for year of birth via matching) and parsimonious (i.e., only covariates that changed the OR by 10% or more) (see Supplemental Material, "Intermediate analyses of association and correlation to identify covariates and confounders for model building"). If two covariates were highly correlated (Spearman $\rho > 0.80$ or χ^2 $p < 0.05$) and led to model convergence problems, one was selected for use based on public health relevance (e.g., though both representing socioeconomic status, an individual-level measure of socioeconomic status such as maternal use of food stamps may be more relevant to a child's health outcome than their census tract–level median household income) and distribution in the population (e.g., heterogeneity of exposure). We considered several individual- and community-level variables that are proxy measures of socioeconomic status, including maternal education, maternal participation in WIC, census tract–level median household income, and census tract–level SVI. The parsimonious models included maternal race and maternal participation in WIC. As a sensitivity analysis, we constructed a third highly adjusted model that included those covariates that were either associated with the exposure or outcome based on χ^2 and Fisher's exact tests at a less stringent $p < 0.20$ (Supplemental Material, "Intermediate analyses of association and correlation to identify covariates and confounders for model building") or had known etiological or biological importance according to the literature (infant sex, mode of delivery).

Results

Demographics

Cases and controls were similar with respect to sex, gestational age, birth weight, mode of delivery, educational attainment of the mother, census tract–level median household income, and SVI (Table 1). Mothers were predominantly non-Hispanic (91% of both cases and controls) and White, but there was a higher percentage of White mothers among cases (81% of cases and 73% of controls). The case group had a significantly smaller percentage of Black mothers (7% in comparison with 16% of controls). A slightly greater frequency of mothers of cases reported participating in WIC (40% of cases and 36% of controls). Case children had a greater percentage of cropland within 500 m of their birth address on average than control children (13.8% in comparison with 12.5%). Average annual $PM_{2.5}$ levels were not significantly different between cases and controls ($11.7\ \mu g/m^3$ for both groups).

Table 2. Exposure prevalence in 405 childhood acute lymphoblastic leukemia cases and 2,080 age-matched controls across exposure windows, metrics, and buffer sizes.

Exposure metric and buffer size	Primary window: Cases ($n = 405$) n (%)	Primary window: Controls ($n = 2{,}080$) n (%)	Perinatal window: Cases ($n = 405$) n (%)	Perinatal window: Controls ($n = 2{,}080$) n (%)
ID^2W 2 km				
Exposed	14 (3)	37 (2)	7 (2)	13 (1)
Unexposed	391 (97)	2,043 (98)	398 (98)	2,067 (99)
ID^2W 5 km				
Exposed	31 (8)	122 (6)	18 (4)	61 (3)
Unexposed	374 (92)	1,958 (94)	387 (96)	2,019 (97)
ID^2W 10 km				
Exposed	59 (15)	270 (13)	41 (10)	153 (7)
Unexposed	346 (85)	1,810 (87)	364 (89)	1,927 (83)
ID_{ups} 2 km				
Exposed	6 (2)	16 (1)	3 (1)	5 (1)
Unexposed	399 (98)	2,064 (99)	402 (99)	2,075 (99)
ID_{ups} 5 km				
Exposed	12 (3)	43 (2)	6 (1)	21 (1)
Unexposed	393 (97)	2,037 (98)	399 (99)	2,059 (99)
ID_{ups} 10 km				
Exposed	18 (5)	74 (4)	12 (3)	39 (2)
Unexposed	346 (95)	1,810 (96)	393 (97)	2,041 (98)

Note: Exposure for each buffer size and metric was dichotomized due to low exposure prevalence. ID^2W, inverse distance-squared weighted well count; ID_{ups}, inverse distance to the nearest upgradient UOG well; UOG, unconventional oil and gas.

UOGD Exposure within the Study Population

A total of 85%–98% of the study population was unexposed to UOGD; the prevalence of unexposed varied based on exposure metric buffer sizes (Table 2). Due to the low prevalence and limited variability in UOGD exposure, we dichotomized our exposure assessment metrics, because there was insufficient spread to apply them with more than two categories or use them continuously. The ID^2W metric, when dichotomized, effectively represents whether the participant had at least one UOG well within the buffer zone, whereas the ID_{ups} metric represents whether the participant had at least one UOG well within the buffer zone that was located upgradient within their watershed.

Residential Mobility

A total of 58% of cases moved residences between birth and diagnosis. The mean distance moved was 9.02 km (median: 0.49 km, interquartile range: 0–4.88 km, range: 0–374 km). Though the proportion of cases who moved (and for some, the distance moved) was substantial, <2% of individuals changed exposure designation (either exposed to unexposed or vice versa) using any metric after the move.

Association between ALL and Exposure to UOGD

Aggregate metric (ID^2W). Using the aggregate UOG exposure metric and the primary exposure window, ORs were elevated for individuals living within 2, 5, and 10 km of UOGD (Figure 2). In models adjusting only for year of birth, the odds of developing ALL were 1.98 times higher in children with at least one UOG well within 2 km of their birth residence, in comparison with those with no UOG wells (95% CI: 1.06, 3.69). The magnitude of the minimally adjusted OR decreased monotonically but remained elevated as the buffer size of the exposure metrics increased to 5 km (OR = 1.33; 95% CI: 0.88, 2.00) and 10 km (OR = 1.14; 95% CI: 0.84, 1.55). After adjusting for maternal race and WIC participation in our parsimonious models, the odds of ALL were 1.74 times higher for individuals living within 2 km of UOGD (95% CI: 0.93, 3.27), with some attenuation of the odds ratio at buffer sizes of 5 km (OR = 1.18; 95% CI: 0.78, 1.78) and 10 km (OR = 1.03; 95% CI: 0.75, 1.40). Our sensitivity analysis, which included adjustment for the additional covariates of sex, delivery route, birth weight, and percentage cropland, did not appreciably change the estimates in comparison with the parsimonious model (Supplemental Material, "Sensitivity analysis using the highly adjusted model").

For the aggregate metric and the perinatal window, estimates were larger in magnitude by 20%–40% than the estimate for the corresponding buffer size using the primary window (Figure 2). Children living within 2 km of UOGD had 2.80 times the odds of developing ALL (95% CI: 1.11, 7.05) in models adjusting only for year of birth. The minimally adjusted odds of ALL were also elevated for children with UOGD within 5 km (OR = 1.54; 95% CI: 0.90, 2.63) and 10 km (OR = 1.42; 95% CI: 0.99, 2.04). In parsimonious models, children with UOGD within 2 km had 2.35 times the odds of having ALL (95% CI: 0.93, 5.95). In sensitivity analyses, the highly adjusted model results were consistent with the parsimonious models at all buffer sizes (Supplemental Material, "Sensitivity analysis using the highly adjusted model").

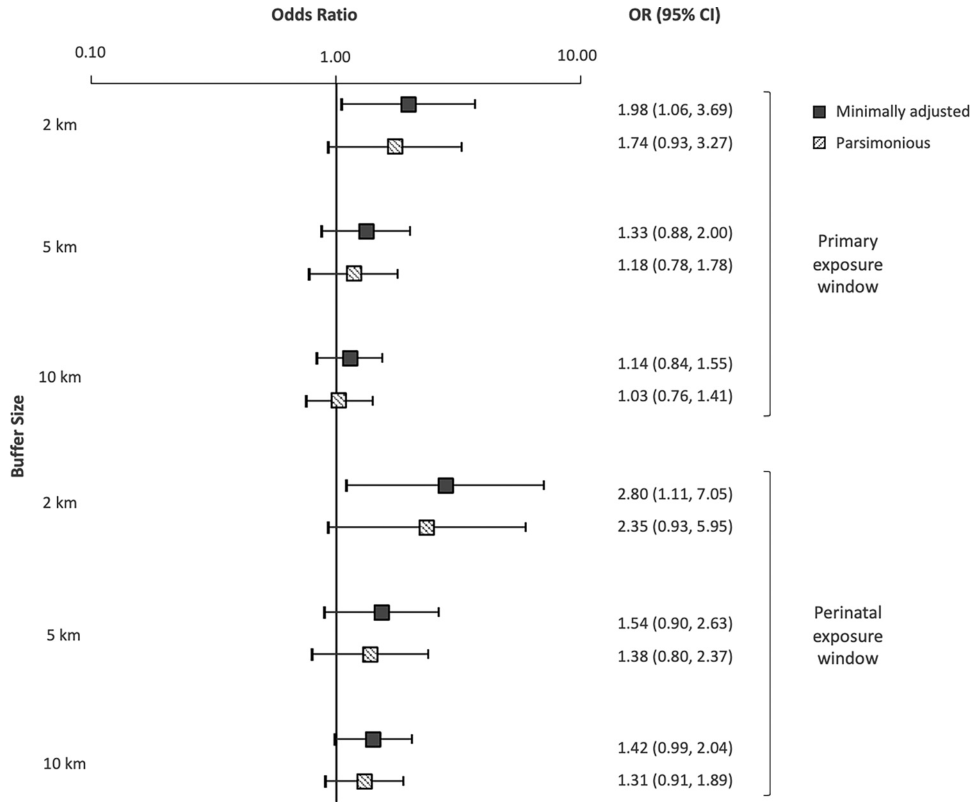

Figure 2. Plots of the risk of childhood acute lymphoblastic leukemia (ORs and 95% CIs) by buffer size, assessed with the aggregate metric for the primary and perinatal exposure windows. The aggregate metric refers to ID^2W well counts. ORs and 95% CIs calculated using unconditional logistic regression. Minimally adjusted: adjusted for year of birth only; Parsimonious: adjusted for year of birth, maternal race, and WIC. Note: CI, confidence interval; ID^2W inverse distance-squared weighted; OR, odds ratio; WIC, Supplemental Nutritional Program for Women, Infants, and Children.

Water pathway-specific metric. Use of the water pathway-specific exposure metric in the regression models produced results that were similar to those for the aggregate metric for the primary exposure window (Figure 3). Children who had at least one upgradient UOG well within 2 km had 1.94 times the odds of developing ALL (95% CI: 0.75, 4.99) in comparison with unexposed children in models adjusting only for year of birth, though the CI was wide. The association was slightly attenuated by adjusting for maternal race and WIC participation (OR = 1.70; 95% CI: 0.66, 4.41), and the most adjusted model results were consistent with the parsimonious model. Children with at least one upgradient UOG well within 5 km had 1.45 times the odds of developing ALL (95% CI: 0.76, 2.77). Finally, children with at least one upgradient UOG well within 10 km in their watershed had 1.26 times higher odds of developing ALL than unexposed children (95% CI: 0.75, 2.14). Adjusting for maternal race and WIC participation attenuated this association (OR = 1.10; 95% CI: 0.64, 1.87). The estimates produced by the sensitivity analyses were not appreciably different from those produced by the parsimonious model (Supplemental Material, "Sensitivity analysis using the highly adjusted model").

The ORs for the water pathway-specific metric restricted to the perinatal window were also similar to those produced by the aggregate metric (Figure 2). In models adjusting only for year of birth, children with UOG activity within 2 km falling within their upgradient watershed had 3.10 times the odds of developing ALL (95% CI: 0.74, 13.01). In the parsimonious model, the odds of developing ALL for those children were 2.45 (95% CI: 0.58, 10.37). Children with an upgradient UOG well within 5 and 10 km had 1.48 and 1.60 times higher odds, respectively, of developing ALL than control children (95% CI: 0.59, 3.68 and 0.83, 3.08, respectively). The odds remained elevated at 5 and 10 km in the parsimonious model. Sensitivity analyses adjusting for additional covariates including sex, delivery route, birth weight, and percentage cropland did not significantly change the estimates in comparison with the parsimonious model (Supplemental Material, "Sensitivity analysis using the highly adjusted model").

Discussion

In this population-based case–control study of UOGD including 405 children with ALL and 2,080 age-matched controls in Pennsylvania, we found that children living in proximity to UOGD had up to 2–3 times the odds of developing ALL. Although ORs were statistically significant in models only accounting for year of birth, elevated ORs persisted after additionally adjusting for race, socioeconomic status, and competing environmental exposures. However, low exposure prevalence limited our statistical power, and confidence intervals at the 2 km buffer size and for the water pathway-specific metric in particular were wide. Nonetheless, our results indicate that exposure to UOGD may be an important risk factor for ALL, particularly for children exposed *in utero.* To our knowledge, this is the first case–control study of childhood ALL that examined UOGD exposure exclusively, the largest study of unconventional oil and gas and hematological malignancies in children, and the first study to apply a water pathway-specific metric of UOGD exposure in a health context.

Our results complement those reported by the McKenzie et al. study in Colorado, which reported significantly elevated odds of ALL for children and young adults ages 5–24 y and nonsignificantly elevated or mixed odds for children ages 0–4 y.[62] In the Colorado study, the strongest odds were observed for children and young adults ages 5–24, who were 3–4 times as likely to live

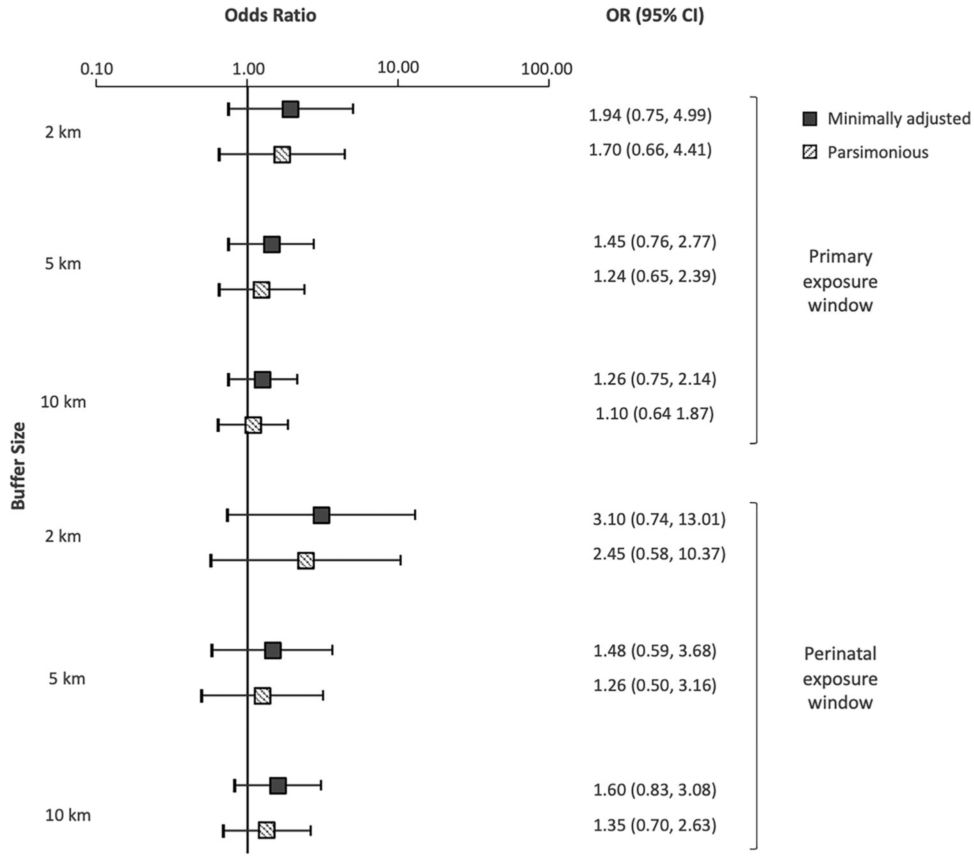

Figure 3. Plots of the risk of childhood acute lymphoblastic leukemia (ORs and 95% CIs) by buffer size, assessed with the water pathway-specific metric for the primary and perinatal exposure windows. ORs and 95% CIs calculated using unconditional logistic regression. Minimally adjusted: adjusted for year of birth only; Parsimonious: adjusted for year of birth, maternal race, and WIC. Note: CI, confidence interval; OR, odds ratio; WIC, Supplemental Nutritional Program for Women, Infants, and Children.

near UOG as control children with nonhematological cancers. Our ORs fell within a similar range. However, their study only had 39 cases in the 0–4 y age range, which may have hindered their ability to draw inferences for that group. Our results, which focus on children ages 2–7 y, provide more information on this younger age group.

Our results also suggest that preconception to birth is an important etiological window for exposure to UOG and the development of ALL. This finding is consistent with research on other environmental exposures, such as pesticides,[25,26,94] bolstering the evidence for the importance of this sensitive window. ORs calculated using the perinatal window were 20%–40% larger than the estimates for the same buffer size using the primary window, though there were fewer exposed individuals and more uncertainty overall. The perinatal period is a critical window for the genetic mutations that precede the development of ALL.[14,15] It is generally hypothesized that the etiology of childhood ALL is multifactorial due to two distinct genetic "hits."[95] The development of preleukemic clone cells commonly occurs after a genetic insult that results in fusion gene formation or hyperdiploidy *in utero*.[2,95,96] Then a second, possibly postnatal, insult is required for overt ALL to develop.[2,4,14,15] Given the similar results observed across both exposure windows, our findings suggest that UOG-related environmental exposures may contribute to both prenatal and postnatal insults leading to the development of ALL.

We applied a new metric for evaluating drinking water exposures from UOGD and identified suggestive relationships between ID_{ups} and ALL. This metric and our selection of buffer sizes were informed by the hydrological and epidemiological literature.[64,65,76,77–81] The estimates generated using the water pathway-specific metric ID_{ups} were similar or greater in magnitude in comparison with estimates using the traditional ID^2W metric, although the uncertainty associated with these estimates was higher. This finding could indicate that water is an important route of exposure to leukemogenic compounds for the development of ALL. Our metrics do not identify specific etiological agents underlying the observed associations. Seventeen compounds used or produced by UOGD have been previously associated with leukemia.[47] One candidate agent is benzene. Maternal occupational and ambient exposure to benzene, which is known to be used or produced by UOGD, in the air[22,32] or in the form of solvents, paints, and petroleum during pregnancy have been associated with elevated odds of ALL.[35] Benzene has been detected in multiple groundwater studies in this region focused on UOGD[41,65,96–99] and in biological samples from communities near oil and gas development.[100] However, it is also possible that these results arose because the water pathway-specific metric produced exposure estimates similar to those of the aggregate metric, particularly when dichotomized. A previous analysis by our group showed that the continuous forms of these metrics tended to be moderately positively correlated with one another (Spearman $\rho = 0.62$ for ID_{ups} and ID^2W at 2 km).[65] It may be that simple proximity to UOGD, which could encompass and/or represent multiple routes of exposure, is the driving factor behind the associations for both metrics. At this time, the dominant stressor is not well understood.[36] Nonetheless, epidemiological studies should try to pinpoint specific exposure pathways underlying associations. Several recent studies of UOGD have explored metrics representing specific (rather than aggregate) routes of exposure, such as flaring, earthquakes, air pollution, and radioactivity.[50,55,101–103]

Epidemiological studies of UOGD exposure have generally relied on spatial surrogates of exposure, such as ID^2W well counts. Previous epidemiological studies using spatial metrics have mainly used a 10 km buffer size or larger.[104,105] However, when considering environmental exposures like water pollution, realistic transport distances should be considered.[106] A study in northeast Pennsylvania measuring the vulnerability of groundwater wells to contamination by UOGD indicates that the extent of a domestic groundwater well's capture zone (the area around the well from which the water is pulled) is generally less than 2 km.[77] Further, Llewellyn et al. suggested that a contaminant plume migrated 1 to 3 km in groundwater from a well pad to domestic wells,[79] and the results of Osborn et al. and Jackson et al. suggest elevated methane levels (i.e., enhanced gas phase transport) within 1 km of UOG well pads.[107,108] Beyond water, an analysis of UOG-related air pollutants found that individuals whose closest UOG well was <0.5 mi (0.80 km) were at greater risk of health effects from exposure to air pollutants than those further than 0.5 mi from a well.[53] The extent of transport of UOG-related air pollutants would be expected to vary by pollutant and local meteorology. Because emitted pollutants attenuate at different functions of distance, there may not be a universal buffer size that optimally captures all hazards. It is possible that applying buffer sizes of 10 km or more could introduce exposure misclassification, dilute the pool of meaningfully exposed individuals, and thus attenuate the magnitude of the observed effect. In this analysis, we observed the largest effect sizes using a buffer size of 2 km, though the number of exposed individuals in these groups was low. The magnitude of the effects at the 5 and 10 km buffer sizes were comparably moderate and was likely particularly apparent in our study because the metrics were used in a binary fashion. Spatial metrics are more typically categorized (e.g., quartiles), and our restricted exposure distribution precluded use of this method. Nonetheless, this attenuation of the observed effect based on the buffer size considered may provide support for using smaller, more selective buffer sizes in epidemiological analyses despite effects to sample size.

This work adds to a growing body of literature on UOGD exposure and women's and children's health used to inform policy, such as setback distances (the required minimum distance between a private residence or other sensitive location and a UOG well).[109,110] Current setback distances in the United States are the subject of much debate,[111,112] with some calling for setback distances to be lengthened to more than 305 m (1,000 ft)[113,114] and as far as 1,000 m (3,281 ft).[115] The current setback distance in Pennsylvania is 152 m (500 ft), extended from 61 m (200 ft) in 2012.[116] We observed elevated odds of cancer associated with UOG activity within 2 km, which exceeds any existing setback distance. Further, although effect sizes diminished with increasing buffer size, the odds of ALL were still elevated at 5 and 10 km buffer sizes. Our results in the context of the broader environmental and epidemiological literature suggest that existing setback distances are insufficiently protective of public health, particularly for vulnerable populations like children, and should be revisited and informed by more recent data.

Our study has several notable strengths. It is the largest study to date investigating UOGD with ALL or any childhood cancer, the first case–control study to focus exclusively on UOGD exposure, and the first to apply a water pathway-specific UOGD exposure metric. We controlled for multiple known risk factors and examined the impact of several competing environmental exposures. We assessed UOGD exposure at multiple buffer sizes informed by the epidemiological and environmental literature. Selection bias, a typical concern in case–control studies, is unlikely to have affected our study because we selected cases from population-based cancer registries and controls from statewide birth records without the need to contact any subjects and seek consent for participation. Because we had access to addresses at two time points for the cases, we were able to examine the potential impact of residential mobility on exposure classification. We determined that only a very small percentage of cases (<2%) had different exposure assignments across birth address and diagnosis address, indicating limited potential for exposure misclassification. This finding is consistent with that of other studies of spatially defined environmental exposures, which also have not found residential mobility to be a major source of error.[82,83]

Our study had several limitations. First, we were constrained by individual-level information available in the birth records, which limited our ability to investigate potential confounders such as parental occupation. Though we designed a statewide study, UOGD is confined to the extent of the shale and drilling is also not performed in urbanized metropolitan centers. Therefore, most of our study population was unexposed. However, we would expect this to have attenuated any observed relationships, because population density and incidence for cancer with nonmodifiable risk factors tends to be higher in urban areas,[117] and urban dwelling individuals may be more likely to experience known risk factors for ALL, such as air pollution.[118,119] Although the ORs were not statistically significant after adjusting for race, socioeconomic status, and other environmental exposures in comparison with ORs from models accounting for year of birth alone, the odds remained consistently elevated across different time periods and metrics. ALL is a rare disease, and as such, the lack of statistical significance could be due more to the rarity of the disease limiting our precision than to lack of biological or public health significance. Low exposure prevalence (between 1% and 5%) when using the water pathway-specific metric (particularly at the smaller buffer sizes) may have reduced model stability and reduced the overall precision of risk estimates. This metric may reveal more differences in larger study populations, or in studies of more common health end points. Moreover, the metric is most relevant for people using private groundwater wells. Although a significant proportion of our suburban and urban population may be served by public water sources, up to 50% of residents in the more heavily drilled rural counties may be served by groundwater wells.[120,121] There is an opportunity to further examine drinking water sources in this population to improve the accuracy of exposure assessment.

Our study suggests that children living near UOGD have increased odds of developing ALL as assessed by multiple metrics, including a novel metric representing drinking water exposure. The magnitude of the association was greatest among those children living within 2 km of UOGD and exposed during the perinatal period. This research adds to a growing body of work documenting adverse health effects associated with UOGD, particularly among children,[36,109,110] and provides additional support for more stringent setback policies and other public health measures to reduce exposures to UOGD.

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ATTACHMENT C

STUDY 5

ENVIRONMENTAL STUDIES

Hydraulic fracturing and infant health: New evidence from Pennsylvania

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The development of hydraulic fracturing ("fracking") is considered the biggest change to the global energy production system in the last half-century. However, several communities have banned fracking because of unresolved concerns about the impact of this process on human health. To evaluate the potential health impacts of fracking, we analyzed records of more than 1.1 million births in Pennsylvania from 2004 to 2013, comparing infants born to mothers living at different distances from active fracking sites and those born both before and after fracking was initiated at each site. We adjusted for fixed maternal determinants of infant health by comparing siblings who were and were not exposed to fracking sites in utero. We found evidence for negative health effects of in utero exposure to fracking sites within 3 km of a mother's residence, with the largest health impacts seen for in utero exposure within 1 km of fracking sites. Negative health impacts include a greater incidence of low–birth weight babies as well as significant declines in average birth weight and in several other measures of infant health. There is little evidence for health effects at distances beyond 3 km, suggesting that health impacts of fracking are highly local. Informal estimates suggest that about 29,000 of the nearly 4 million annual U.S. births occur within 1 km of an active fracking site and that these births therefore may be at higher risk of poor birth outcomes.

INTRODUCTION

The growth in unconventional gas production involving hydraulic fracturing ("fracking") has transformed the energy landscape, reducing energy prices, decreasing conventional air pollution by displacing coal in electricity generation, disrupting international energy trading arrangements, and increasing the prospects for energy self-sufficiency for the United States. At the same time, continuing concerns about the possible local health effects of hydraulic fracturing have led some states and communities to ban the practice altogether. The absence of a systematic evaluation of fracking's health effects has complicated the decision process for those governments around the world who are debating whether to allow hydraulic fracturing.

Hydraulic fracturing could affect human health through several channels, including water and air pollution. In the fracking process, water and other chemicals are forced into shale rock to fracture it and allow the gas or petroleum trapped in the shale to be tapped. Whereas much of the previous research has focused on water pollution (*1*–*3*), several recent studies address the possible effects of chemicals that have been found in both "fracturing fluid" (the fluid that is forced into the shale in order to fracture it) and in air emissions near fractured gas wells (*4*–*6*). One study measured various air pollutants weekly for a year surrounding the development of a newly fractured gas well and detected nonmethane hydrocarbons, methylene chloride (a toxic solvent), and polycyclic aromatic hydrocarbons, which have been shown to affect fetal outcomes (*7*).

There are at least two reasons to focus particularly on infant health in probing the health effects of exposure to hydraulic fracturing. First, there is increasing evidence that the fetus is vulnerable to a range of maternal pollution exposures (*8*–*13*). Second, because the fetus is in utero for at most 9 months, it is possible to pinpoint the timing of potential exposure. This is not the case with other possible health effects, such as cancer, that develop over long periods of time. Moreover, birth data are available with precise information on mothers' residential locations, permitting researchers to examine the effects of proximity to fracturing sites on the health of newborns.

This paper provides evidence for impacts of hydraulic fracturing on human health, based on a large-scale analysis of vital statistics records from more than 1.1 million births in Pennsylvania during the period 2004–2013. Our empirical approach compares infants born to mothers living at different distances from hydraulically fractured well sites, both before and after hydraulic fracturing was initiated at the well site. In addition, we probe the robustness of the results by adjusting the estimates for maternal fixed effects to include comparisons of siblings who were exposed to fracking with those who were not. Further, we explore the relationship between infant health outcomes and residential distance from fracturing sites, comparing birth data from mothers residing at increasing 1-km intervals from the fracturing sites to investigate whether there is a gradient in the effects of exposure.

The results of our analysis suggest that the introduction of fracking reduces health among infants born to mothers living within 3 km of a well site during pregnancy. For mothers living within 1 km, we find a 25% increase in the probability of low birth weight (birth weight < 2500 g) and significant declines in average birth weight and in an index of infant health. There are also reductions in infant health for mothers living within 1 to 3 km of a fracking site, but the estimates are about one-third to one-half of the size of those within the 0- to 1-km band. There is little evidence of health effects at further distances, suggesting that health impacts are highly local.

This paper addresses four problems that have plagued the previous literature (*14*–*16*). First, the sample size of this analysis is much larger than that used in previously published work. Second, in addition to examining low–birth weight status, which is the most commonly used measure of infant health in the literature, we use an index of infant health outcomes informed by the literature on multiple hypothesis testing (*17*, *18*) to incorporate the many other measures of infant health that are available in the vital statistics data. Third, we test for effects at various distances of maternal residence from fracking sites, rather than imposing one arbitrary assumption about the distance where health impacts may become apparent, or about the functional form of the distance gradient.

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An additional innovation is that our models control for mother fixed effects. Estimates of fracking-independent aspects of maternal health in these models are controlled by comparing the health of fracking-exposed and unexposed siblings born to the same mother. In principle, this comparative technique controls for all the unobserved time invariant characteristics of the mother such as race that could confound conventional difference-in-differences estimates (that is, before and after comparisons of places with and without fracking). However, in practice, the mother fixed effects estimates are imprecise because there are relatively few sibling pairs with an exposed and an unexposed sibling even when we are examining all Pennsylvania births.

RESULTS AND DISCUSSION

Figure 1 shows both the geographical distribution of births in Pennsylvania from 2004 to 2013 and the locations of fractured wells across the state. The greatest number of births occurs in the southeast of the state near Philadelphia, whereas fractured wells follow the state's shale deposits along a diagonal path from the northeast to the southwest of the state. Although many areas with fracturing are lightly populated, the areas surrounding Pittsburgh have a high population density in addition to many fractured wells. Figure 2 illustrates the temporal distribution of fractured wells, showing that most new wells came online after 2009. Although the number of new wells peaked at the beginning of 2012, the amount and economic value of gas production continued to grow over our sample period.

Table 1 explores differences in maternal characteristics, infant characteristics, and health outcomes between mothers who were potentially exposed to fracturing and those who were not. The first two columns show variable means for mothers whose residences were less than 1 km from a location (or multiple locations) that fractured. Columns (3) and (4) report the means for births to mothers who live within 3 to 15 km of a well location. These samples are further divided into those whose infants were born before the spud date (that is, the commencement of drilling)—thus, never exposed to fracking—and those whose babies were born after the spud date. When the mother is within 1 km of multiple locations, we use the earliest spud date to align with the approach used in the regression analysis.

The remaining columns, (5) to (7), report *P* values from tests that the means are equal across the pairs of columns indicated in the row headings. These tests help shed light on the credibility of different approaches to measuring the infant health effects of fracking exposure. Column (5) reports *P* values for *t* tests of the hypothesis that the means are equal within 0 to 1 km of a well location before and after the spud date. These comparisons indicate that mothers whose babies were potentially exposed to nearby fracturing in utero are younger, less likely to have been married at the time of the birth, and less educated—characteristics that might lead to worse infant health outcomes even in

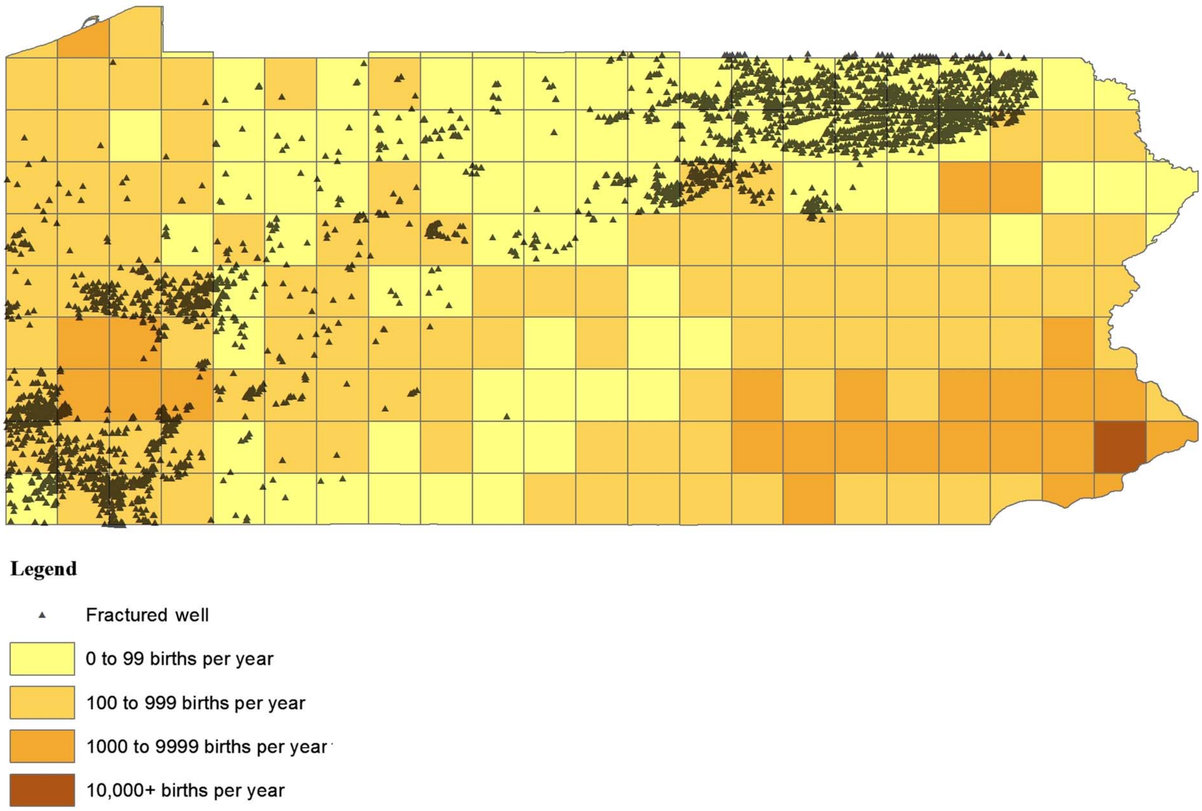

Fig. 1. Locations of births and fractured wells in Pennsylvania. Each square displayed above is 0.25° latitude by 0.25° longitude. We use all birth certificates in Pennsylvania for 2004–2013. They include maternal address which is used to calculate average yearly births per square. Black triangles represent the exact locations of fractured wells, which we observe from the Pennsylvania Department of Environmental Protection (DEP) Internal Operator Well Inventory. These data include all oil and gas wells with a Pennsylvania DEP drilling permit and which are not currently filled in (plugged). We queried this database in November 2014. Fractured wells are those marked "unconventional" in the database. We have dropped any wells with missing American Petroleum Institute numbers, spud or permit date, or location information.

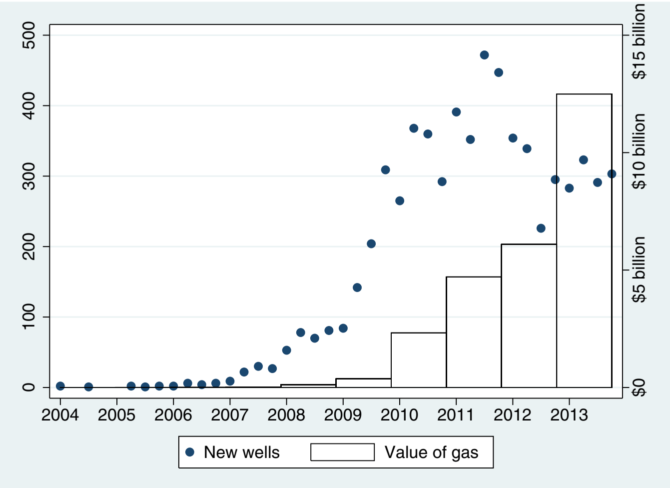

Fig. 2. Number of fractured wells and value of all drilling in Pennsylvania (2004–2013). The left *y* axis shows total fractured wells in Pennsylvania by spud year and quarter (that is, the commencement of drilling), and the right *y* axis reports annual values of gas from fractured wells in Pennsylvania. *X* axis shows spud year and month (dates of commencement of drilling) that are recorded in the Pennsylvania DEP Internal Operator Well Inventory, which is described in the notes to Fig. 1. Annual gas production per well is recorded by the Pennsylvania DEP in its Oil and Gas Historical Production Report. We merge these data to our Internal Operator Well Inventory data by well identification number and then sum gas production to the year level. To convert production to dollars, we use gas prices from the U.S. Energy Information Administration (EIA), which reports the Henry Hub Natural Gas Spot Price (www.eia.gov/dnav/ng/hist/rngwhhdA.htm). To convert to British Thermal Units annual heating values for Pennsylvania are taken from the EIA.

the absence of fracturing. Column (6) reveals that there are also significant changes in the characteristics of infants and mothers who live 3 to 15 km from a fractured well site after the spud date, relative to before. One of the most marked differences is that the fraction of births to black mothers is much lower in this distance category after fracturing begins (and the fraction of births to white mothers is correspondingly higher). This difference arises because over time, more wells were drilled near urban areas such as Pittsburgh, where higher numbers of African Americans live.

A potentially valid approach to estimating the effects of fracturing is to use a difference-in-differences estimator that compares "before versus after" in the area near fracturing to "before versus after" in areas far from a fracturing site. This approach requires that all determinants of infant health except fracturing evolve identically in the areas near and far from fracturing. Column (7) provides an opportunity to gauge the credibility of this approach. It reports the *P* value from a test of the hypothesis that the difference between the column (1) and (2) means is equal to the difference between the column (3) and (4) means. The results show that using difference-in-differences reduces the potential for confounding fracking exposure with other determinants of infant health, but important differences in the evolution of marriage rates, race, education, and age remain. Although we control for all the observable factors in our models, these differences suggest that there may also be unobserved differences across areas in other factors that could influence infant health. This observation motivates the inclusion of mother fixed effects in the equation of outcomes as a function of potential exposure to a fractured well as shown in Eq. 2 (see Materials and Methods).

Figures 3 and 4 provide an opportunity to investigate the relationship between distances from a fracked well and measures of infant health. These figures are based on estimation of Eq. 1 (see Materials and Methods), except that "Near" is treated as a vector of indicators for each 1-km distance increment from a well site, as

Table 1. Difference in means. The data source is the universe of birth certificates in Pennsylvania (2004–2013) matched to the Pennsylvania DEP Internal Operator Well Inventory. Maternal and infant demographic indicators and health outcomes are recorded at the time of birth. "Near, 0–1 km" indicates that the mother lives within 0 to 1 km of at least one well site. "Far, 3–15 km" indicates that the mother lives 3 to 15 km from the nearest well site. Columns (5) to (7) report *P* values from *t* tests of equality of means across the different samples indicated. Column (7) tests whether (2) − (1) = (4) − (3). This quantity is referred to as the difference-in-differences, or D-in-D.

	Near, 0–1 km		Far, 3–15 km		*P* values		
	Before	After	Before	After	(5)	(6)	(7)
	(1)	(2)	(3)	(4)	(1) − (2)	(3) − (4)	D-in-D
Mother characteristics							
Married	0.68	0.61	0.62	0.63	0.00	0.00	0.00
Black	0.01	0.02	0.12	0.06	0.01	0.00	0.00
Hispanic	0.01	0.01	0.02	0.02	0.66	0.00	0.57
<High school	0.11	0.12	0.11	0.10	0.27	0.00	0.01
High school	0.28	0.31	0.26	0.25	0.02	0.00	0.00
Some college	0.32	0.32	0.28	0.29	0.89	0.00	0.43
College	0.22	0.17	0.22	0.23	0.00	0.00	0.00
Advanced	0.08	0.08	0.13	0.13	0.74	0.69	0.74
<20 years old	0.06	0.06	0.06	0.05	0.89	0.00	0.11
20–24 years old	0.21	0.26	0.22	0.21	0.00	0.00	0.00
25–29 years old	0.30	0.31	0.29	0.29	0.42	0.00	0.86
30–34 years old	0.26	0.23	0.27	0.28	0.01	0.00	0.00
>35 years old	0.17	0.14	0.17	0.16	0.01	0.00	0.07
Infant characteristics							
Male	0.50	0.52	0.51	0.52	0.24	0.27	0.32
First born	0.42	0.41	0.43	0.43	0.66	0.15	0.84
Second born	0.33	0.34	0.33	0.33	0.46	0.05	0.68
Third born	0.16	0.16	0.15	0.15	0.79	0.64	0.73
Fourth and up	0.09	0.09	0.09	0.09	0.90	0.51	0.98
Health outcomes							
Low birth weight	0.05	0.07	0.06	0.06	0.04	0.00	0.01
Birth weight	3354.35	3312.81	3316.94	3331.08	0.01	0.00	0.00
Health index	0.05	0.01	0.01	0.02	0.01	0.00	0.00
n	4871	1798	133,107	78,366			

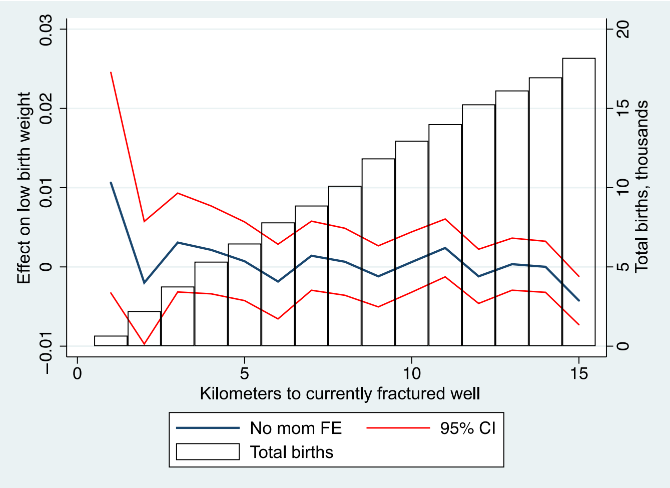

Fig. 3. Effect of fracturing on low–birth weight, county fixed effects. The left *y* axis of the graph indicates coefficients and confidence intervals (CIs) from a version of Eq. 1 in which "Near" is replaced with 15 distance indicators representing the proximity of maternal residence to well sites; the coefficients represent the in utero effect on infant health of hydraulic fracturing (that is, when conception occurs after well spud date) at 1-km intervals from the well site. The data sources for the regression are all birth certificates issued in Pennsylvania from 2004 to 2013 and the Pennsylvania DEP Internal Operator Well Inventory. We exclude births with missing values for gestation length or latitude/longitude of maternal residence. We calculate the distance between maternal residence and well sites using Vincenty's formula. The specification includes year fixed effects (FE), month of birth FE, and county of maternal residence FE. The following demographic controls are also included: mother is married, marital status missing, maternal race and ethnicity (black, Hispanic, missing), maternal education [no high school (HS), HS diploma, some college, college, advanced degree, missing], maternal age (<20, 20 to 24, 25 to 29, 30 to 34, 35+, missing), child is male, child sex missing, and child parity (first, second, third, fourth born and higher, parity missing). Standard errors are clustered on maternal ID. The right *y* axis plots average yearly births at each distance from a well site.

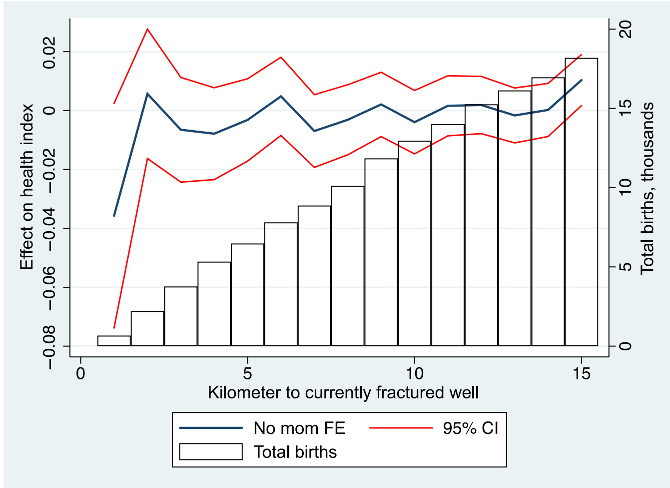

Fig. 4. Effect of fracturing on infant health index, county fixed effects. The left *y* axis of the graph indicates coefficients and CIs from a version of Eq. 1 in which "Near" is replaced with 15 distance indicators representing the proximity of maternal residence to well sites; the coefficients represent the in utero effect on infant health of hydraulic fracturing (that is, conception occurs after well spud date) at 1-km intervals from the well site. The data sources for the regression are the universe of birth certificates issued in Pennsylvania from 2004 to 2013 and the Pennsylvania DEP Internal Operator Well Inventory. We exclude births with missing values for gestation length or latitude/longitude of maternal residence. We calculate the distance between maternal residence and well sites using Vincenty's formula. The infant health index ranges from 0 to 1; an increase indicates better health. The regression specification includes year FE, month of birth FE, and county of maternal residence FE. The following demographic controls are also included: mother is married, marital status missing, maternal race and ethnicity (black, Hispanic, missing), maternal education (no HS, HS diploma, some college, college, advanced degree, missing), maternal age (<20, 20 to 24, 25 to 29, 30 to 34, 35+, missing), child is male, child sex missing, and child parity (first, second, third, fourth born and higher, parity missing). Standard errors are clustered on maternal ID. The right *y* axis plots average yearly births at each distance from a well site.

described above. The unaffected group is composed of births to mothers living more than 15 km away from a well site. The figure also shows the number of births in each distance category.

On the basis of these figures, we conclude that any significant effects of fracking exposure occur within 3 km of a well site. It is also evident that the largest effects are concentrated within 1 km of the fracking site. For example, Fig. 3 shows that the coefficient on the indicator for maternal residence within 1 km of a site is approximately 0.01, indicating a 0.01 percentage point increase in the probability of low birth weight relative to people who live 15 km or more away from a site. The effect of living 1 to 2 km from a site is near zero, but the effect of living 2 to 3 km from a site again appears to be positive. Figure 4 suggests that the infant health index is worse at 0 to 1 km from a fracking site than at higher distances. There is some unavoidable arbitrariness in defining the cutoff at 3 versus 4 km; however, it is nevertheless evident from our data that there is little justification for including births at further distances in the potentially affected group.

Table 2 reports the results that emerge from the estimation of Eqs. 1 and 2. The first three columns use 0 to 1 km as the definition of "Near," the next three columns use 1 to 2 km, and the last three columns use 2 to 3 km. In each case, the unaffected group is mothers who live 3 to 15 km from a site. Hence, we compare mothers at 0 to 1 km to mothers at 3 to 15 km, mothers at 1 to 2 km to mothers at 3 to 15 km, etc. In each group of three columns, the first column reports results from fitting Eq. 1 on the entire sample. In columns (2) and (3), the sample is restricted to births from mothers who live within 15 km of a well site, and these columns report on results from Eqs. 1 and 2, respectively. Each row corresponds to a different birth outcome, so that each entry in the table is a separate estimate of coefficient a_2. Note that because the omitted group is held constant in the regressions (it is always the mothers who are greater than 3 km and less than 15 km from a site), the regressions are not directly comparable to Figs. 3 and 4. In Table 2, the standard errors are clustered by mother. We have also estimated alternative models clustering by county, which yields very similar patterns.

Column (1) suggests that maternal residence within 1 km of an active well site that was hydraulically fractured before conception is associated with significantly worse infant health outcomes than are more distant locations. The estimated effect on the probability of low birth weight is large (0.016), relative to the baseline mean incidence of low birth weight of 0.065. We also estimate a small but statistically significant negative effect on mean birth weight of about 39 g. It is quite common in the pollution and health literature to find a larger effect of pollution on low–birth weight incidence than on average birth weight (*10*–*13*); this finding is consistent with the possibility that any effects are concentrated among lighter, likely more vulnerable, infants. Finally, the infant health index also suggests a relatively small but statistically

Table 2. Effect of fracturing on infant health. Each coefficient and SE (shown in parentheses) is from a different regression and represents the effect on the given infant health outcome of in utero exposure to fracturing (when conception occurs after well spud date) within the indicated distance. The data sources for the regression are all birth certificates issued in Pennsylvania from 2004 to 2013 and the Pennsylvania DEP Internal Operator Well Inventory. We calculate the distance between maternal residence and well sites using Vincenty's formula. The infant health index ranges from 0 to 1; an increase indicates better health. Each regression specification includes region of maternal residence*year FE, year*month of birth FE, and county of maternal residence FE. The following demographic controls are also included: mother is married, marital status missing, maternal race and ethnicity (black, Hispanic, missing), maternal education (no HS, HS diploma, some college, college, advanced degree, missing), maternal age (<20, 20 to 24, 25 to 29, 30 to 34, 35+, missing), child is male, child sex missing, and child parity (first, second, third, fourth born and higher, parity missing). Where indicated, we include a vector of maternal ID fixed effects ("mother FE"). "Under 15 km" indicates the subset of mothers living less than 15 km from the nearest well site. SEs are clustered on maternal ID. $^{+}P < 0.10$; $^{**}P < 0.05$; $^{***}P < 0.01$.

	(Near, 0–1 km) × after			(Near, 1–2 km) × after			(Near, 2–3 km) × after		
Dependent variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Low birth weight	0.016**	0.015**	0.012	0.006+	0.005	0.004	0.009***	0.008***	0.007
(mean, 0.065)	(0.007)	(0.007)	(0.014)	(0.004)	(0.004)	(0.007)	(0.003)	(0.003)	(0.005)
Birth weight	−38.654**	−36.707**	−13.034	−3.534	−2.023	−10.439	−7.092	−5.294	0.803
(mean, 3319.6)	(15.558)	(15.595)	(31.137)	(8.487)	(8.530)	(14.349)	(6.515)	(6.575)	(10.608)
Health index	−0.054***	−0.052***	−0.004	−0.020**	−0.018+	−0.018	−0.028***	−0.025***	−0.015
(mean, 0.000)	(0.019)	(0.019)	(0.040)	(0.010)	(0.011)	(0.020)	(0.008)	(0.008)	(0.015)
n	1,086,917	231,578	231,578	1,102,424	247,085	247,085	1,117,919	262,580	262,580
Mother FE	No	No	Yes	No	No	Yes	No	No	Yes
Under 15 km	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes

significant decline in health; the coefficient of −0.054 means that births near a well site where hydraulic fracturing began before conception have a −0.054 standard deviation decline in the health index. Limiting the sample to births to mothers living within 15 km, as shown in column (2), has little effect on the estimates, despite the sharp reduction in sample size.

Column (3) reports the estimates from fitting the mother fixed effect specification (that is, Eq. 2) on the 15-km sample. The inclusion of mother fixed effects is very demanding of the data, a circumstance reflected in SEs, which are about twice as large as those in columns (1) and (2); this increased SE arises because, within the 0- to 1-km range, only 594 of the 1798 potentially exposed infants [see column (2) of Table 1] have an unexposed sibling in the data. At 2 to 3 km, 10,568 infants are potentially exposed and 3538 have a sibling in the data—a better statistical situation than the 0- to 1-km cohort, but still a tiny fraction of the overall number of births. The pattern of the coefficients remains qualitatively similar, particularly for the incidence of low birth weight.

The remaining columns report on the same three specifications, except that to test the robustness of our results to different definitions of "Near," the "Near" group is defined as those living within a 1- to 2-km radius of a well site in columns (4) to (6) and a 2- to 3-km radius from a site in columns (7) to (9). These estimates indicate negative health effects from fracking, although they are smaller than in the 0- to 1-km range. For example, the estimated effects on the incidence of low birth weight and on the infant health index are about one-third to one-half of the effect size in the 0- to 1-km category. The effects on birth weight are smaller and statistically insignificant. When maternal fixed effects are added to the models, the estimates are qualitatively similar, although generally somewhat smaller, but the increase in the SEs means that these estimates are not statistically significant by conventional criteria.

We additionally conducted a series of robustness checks. A potential concern is that the analysis is based entirely on a list of wells that were active in 2014 and that therefore does not include hydraulically fractured wells that were no longer active as of that date. These wells were not included because the well data set includes the spud date for these wells but does not report when the well became inactive. Hence, our baseline analysis could underestimate exposure if the wells were active during a woman's pregnancy but shut down sometime after an infant's birth. As a check, we reestimated the models using the full sample of wells, active and inactive; the results are essentially unchanged as shown in table S2.

A further issue is that we have assigned "Exposure" on the basis of whether conception occurred after the spud date. Hence, there are some women for whom drilling occurred during a pregnancy that began before the spud date, and these women are treated as not having been exposed. If these women were negatively affected, then the estimates may understate the health effects of fracturing. Conversely, if it is exposure in the earliest days of the pregnancy that matters, then the impacts will be smaller for infants who were only exposed later in the pregnancy, and adding these infants to the "exposed" sample will reduce the estimated effects. Therefore, we reestimated the models defining "Exposure" on the basis of whether the birth (rather than the conception) occurred after the spud date. Table S3 reveals that these estimates are generally slightly smaller than those in Table 2, suggesting that infants exposed early in the pregnancy may suffer the most harm; however, the sampling variability makes definitive judgments difficult.

We have also tried adding additional controls for area interacted with year to allow for secular changes in infant mortality that vary at a very local level. Specifically, because counties are of varying size, we overlaid a grid based on 0.5° of longitude and 0.5° of latitude over the state of Pennsylvania and estimated a model that included an indicator for the square in which the mother resides interacted with year of conception. These results are shown in table S4 and are qualitatively unchanged, compared to those discussed above.

In table S5, we attempt to investigate the effects of intensity of exposure in the area within 1 km of a residence. For mothers living within 1 km of a well site, the median number of well sites is 2. Hence, we alter our main specification to distinguish between the effect of having at least one active well and the effects of having more than two active wells. This is a demanding test of the data, and we are unable to reject the null hypothesis that the effects are equal for births exposed to above the median and below the median number of wells.

Finally, the probability of a low–birth weight birth is only 6.5% in this sample. Of relevance to this point, all the estimates have come from linear probability models; given the relatively low mean, it may be more appropriate to rely on nonlinear estimation approaches. Table S6 reports the marginal effects from logit estimation of Eq. 1 on the 15-km sample and finds that the results are qualitatively similar to those from the linear probability model in Table 2.

CONCLUDING REMARKS

This paper provides evidence of effects of exposure to hydraulic fracturing on infant health, using a large-scale analysis of vital statistics records from more than 1.1 million births in Pennsylvania during the 2004–2013 period. Overall, the results suggest that the introduction of fracking reduces health among infants born to mothers living within 3 km of a well site during pregnancy. We find the largest effects for mothers living within 1 km of a site—a 25% increase in the probability of a low–birth weight birth (<2500 g) and significant declines in average birth weight, as well as in an index of infant health. There are also reductions in infant health for mothers living within 1 to 3 km of a fracking site, but the estimates are about one-third to one-half of the size of those for mothers within the 0- to 1-km band. There is little evidence of health effects at further distances, suggesting that health impacts are highly local.

What do these estimated impacts imply for the affected infants? Studies based on large administrative databases have consistently shown that low birth weight is a risk factor for numerous negative outcomes, including infant mortality, attention deficit hyperactivity disorder, asthma, lower test scores, lower schooling attainment, lower earnings, and higher rates of social welfare program participation (*19*, *20*). For example, one large-scale study of twin pairs in Norway found that a 10% difference in birth weight in their predominantly low–birth weight pairs was associated with a 1% difference in the probability of graduating from high school and a 1% difference in earnings, with outcomes all being better for the higher-weight twin (*20*).

Are these effects large or small relative to those found in other studies? Many other studies examine the effects of exposure to criterion air pollutants, such as carbon monoxide or nitrous oxides, rather than the specific types of hazardous air pollutants that have been noted near some fracking sites (*4*–*7*). For example, a study of the installation of EZ Pass toll plazas in New Jersey and Pennsylvania showed that EZ Pass was associated with reductions of 40% in CO and 11% in NO, which in turn reduced the incidence of low birth weight by 12% among mothers living within 2 km of a toll plaza (*13*). A recent study of openings and closings of industrial plants that emit hazardous air pollutants, such as benzene (one of the chemicals that has been found near fracking sites), suggested that plant operation is associated with a roughly 3% increase in the incidence of low birth weight among mothers within 1.6 km (1 mile) of the plants (*12*). Thus, this paper's estimated findings of a 25% increase in the probability of a low–birth weight birth within 1 km and smaller effects at larger distances are not inconsistent with the findings that have been reported in previous studies of the effects of air pollution on fetal health.

Available data sources allow for some rough estimates of the number of births in the United States annually that are at risk from fracking. Specifically, we combined data from the National Center for Health Statistics (NCHS) on the number of births by county from July 2012 through June 2013, with data on the number of fractured wells in 2012 from HPDI, an information services company in the energy industry. The NCHS data are only available by county (whereas our Pennsylvania birth data have women's exact addresses), but by assuming a uniform distribution of population across counties, we can estimate the number of births to women within 1 km of an active well that was hydraulically fractured in that year. Although the HPDA data do not have a fracking indicator, we infer it by using information on which wells are in tight oil or shale gas plays; hydraulic fracturing is generally required for the efficient recovery of oil and gas in these areas. These calculations suggest that as many as 65,000 infants were potentially exposed nationally in this 1-year period because their mothers live within 1 km of a well site that is likely to have been fractured.

The superior data available in Pennsylvania allow us to compare the estimated number of births exposed to the actual number of infants exposed to fracking during gestation. This comparison suggests that the assumption of a uniform distribution of births across counties leads to substantial overestimates of the number of infants born within 1 km of an active well site that was fractured; presumably, this is because fracking occurs in less populated parts of counties where there are fewer births per square kilometer. When we scale our national estimate downwards using the ratio of estimated to actual exposed births for Pennsylvania, we estimate that approximately 29,000 U.S. infants were exposed (that is, born to mothers living within 1 km of an active well that was fracked) between July 2012 and June 2013. This is about 0.7% of the infants born in the United States over that period.

A limitation of our study is that given the nature of the available data, we are constrained to focus on potential exposure to pollution (which is determined by the mother's residential location) rather than actual exposure that could be measured with personal monitoring devices. In principle, future research could measure the types and amounts of chemicals emitted by hydraulic fracturing, the distance that those chemicals are transported under normal weather conditions, and the likely effects of those specific chemicals on fetal health and on the health of children and adults.

A second limitation of our study is that even starting with the whole population of Pennsylvania births, we end up with a relatively small sample of children who were potentially exposed to fracking; this small effective sample size limits our ability to probe the shape of the distance-exposure relationship and also limits our ability to obtain precise estimates from models with mother fixed effects.

A third caveat is that the pathway of exposure was not a subject of our study and is not known with certainty. The results of our study are consistent with the possibility that very local air pollution, perhaps from the multiple diesel generators used at well sites, from chemicals used in fracking, or even from truck traffic to and from sites, could be a potential key source of exposure. Previous research regarding human health effects of exposure to hydraulic fracturing has also identified contaminated water as a possible pathway. Although industrial activity from hydraulic fracturing and improper disposal of fracturing fluids can affect water quality, recent analyses suggest that it is not common for fracturing fluids to leak into surface water from the fractured well sites (*1*, *2*). Tighter regulation of fluid disposal and fracturing activities may have mitigated threats to water quality; nevertheless, this potential avenue for deleterious effects on human health effects also deserves careful monitoring.

A fourth caveat is that, to the extent that there are economic benefits of fracking that accrue to women who live less than 1 km from a fracking site, our estimates could understate the specific effects of fracking exposure on human health. If, for example, women living near wells receive income from mineral rights, then the higher income per se could be expected to confer a health benefit, which might partially offset the negative effects of fracking-related pollution.

Finally, future research should focus on a richer set of outcomes, including child health at older ages and adult health. These outcomes can be difficult to track, but creative uses of administrative data may provide compelling opportunities to more thoroughly investigate the local health consequences of exposure to hydraulically fractured well sites.

MATERIALS AND METHODS

The data for this project came from two sources. First, data on all births in Pennsylvania were obtained from the Certificate of Live Births (birth certificates) from 2004 to 2013. These data include a record for every birth, and each record has information about the infant's health at birth as well as latitude and longitude of the maternal residence and maternal characteristics such as race, education, and marital status. Because we used confidential data, our study protocol was vetted by Princeton University's Institutional Review Board. Siblings were matched using the mother's full maiden name, race and birth date, as well as father's information, and social security numbers where available.

There are many possible health outcomes listed on birth certificates, several of which represent rare outcomes. In what follows, we focus on birth weight and low birth weight (birth weight less than 2500 g), which are the most commonly examined measure of fetal health outcomes in the environmental economics literature. Birth weight is commonly examined because it has been the most widely available measure, it is relatively accurately measured, and low birth weight is quite common unlike conditions such as specific congenital anomalies, for example.

We also show estimated effects on a composite infant health index that is constructed to have a mean of 0 and an SD of 1, with positive (negative) values indicating above (below) average infant health (measured in SDs). Our index is suggested by the literature on multiple hypothesis testing (*17*, *18*). If there are k outcomes and Y_k is the kth, then let μ_k be the mean and σ_k be the SD. We normalize our outcomes by subtracting the mean and dividing by the SE: $Y_k^* = (Y_k - \mu_k)/\sigma_k$. The summary index is then $Y^* = \Sigma_k Y_k^*/K$. We construct two versions of this summary index, one using the full sample of births and one using the subsample of births within 15 km of a well. The index is the mean over the standardized outcomes, weighted by the inverse covariance matrix of the transformed outcomes to ensure that outcomes that are highly correlated with each other receive less weight than those that represent new information.

The index is a combination of birth weight in grams and indicators for low birth weight, prematurity (gestation less than 37 weeks), the presence of any congenital anomalies, and the presence of any other abnormal condition of the newborn. The index provides a solution to the challenges to inference from separately examining the multiple measures of infant health (that is, "multiple hypothesis" testing). The problem is that the probability that at least one estimated effect is deemed "significant" increases with the number of tests. Focusing on an index avoids this difficulty. The index is defined so that a larger value indicates more positive health.

We focus on a sample of singleton births because twins and other multiples are generally in poorer health at birth for reasons unrelated to hydraulic fracturing. After excluding births with missing information, we are left with an initial birth sample of 1,125,748 births, of which 270,410 are within 15 km of a site where a fractured well was active in 2014. From the initial sample of 1,449,427 births, we lose the following: 55,337 births that were part of a multiple birth; 25,029 births that were missing values for gestational age, birth weight, congenital anomalies, or abnormal conditions of the newborn; 226,548 births that were missing latitude and longitude; 41,789 births missing a maternal identifier; and 146 duplicate records. The sum of the missing categories above exceeds the number of cases lost because some cases are missing more than one set of variables.

The second source of data is a list of all of the fractured wells that were active in 2014 in the Pennsylvania DEP Internal Operator Well Inventory (*21*). Fractured wells are those marked "unconventional" in the database. For each well, we know the location and the date (month and year) that it was fractured. There are 7757 active fractured wells in our data, the vast majority of which were fractured after 2009. Below, we show that the focus on active wells, rather than all fracked wells, does not alter the results.

To match births to fractured gas wells, we computed the distance from the mother's residence to all locations where fracturing ever took place between 2004 and 2013, regardless of whether the fracturing had yet occurred at the time of the conception. Distances were computed using Vincenty's formula for calculating the distance between two points on a sphere. In our sample, there are 24,148 births to mothers residing less than 2 km from a site where fracturing ever occurred and 6669 living within 1 km of a site where fracturing ever occurred; of this last group, 1798 births were potentially exposed to active fracturing at some point while in utero, because the conception date occurred after the date that drilling was initiated (that is, the spud date).

We estimate several different statistical models with and without sibling comparisons. Some models are estimated using the entire sample of Pennsylvania births, whereas others focus only on births within 15 km of a well site. The latter sample excludes births in Philadelphia, for example, where there is no fracturing and birth outcomes may be changing differentially from those in the rest of the state for reasons unrelated to the proliferation of fracturing.

The first specification that we estimate is

$$\begin{aligned} Y_{it} = {} & a_0 + a_1\mathrm{Near}_i + a_2\mathrm{Exposure}_{it} + a_3\mathrm{X}_{it} + a_4\mathrm{County}_{it} \\ & + a_5\mathrm{Time}_{it} + a_6\mathrm{Regional\_trend}_{it} + e_{it} \end{aligned} \tag{1}$$

where Y_{it} is a birth outcome for mother i in year t. County_{it} is a vector of zero-one indicators for the mother's county of residence at the time of the birth, Time_{it} is a vector of zero-one indicators for the birth month and year (for example, October 2006), and $\mathrm{Regional\_trend}_{it}$ is a region-specific linear time trend based on a division of Pennsylvania into six regions (*22*). The vector X_{it} of observable maternal and child characteristics includes indicators for child gender, maternal race and ethnicity (African-American, Hispanic, missing), mother's age (<20, 20 to 24, 25 to 29, 30 to 34, 35+, missing), mother's education (<high school, high school, some college, college, advanced degree, missing), marital status (including an indicator for missing marital status), and child parity (first, second, third, fourth born or higher, parity missing).

One reason for controlling for parity is that in our data, the exposed sibling tends to be younger than the unexposed sibling in a sibling pair, so that it is important to control for birth order effects.

To develop our measure of exposure, we first define two vectors for each birth, each of which contains a separate element/variable for each well site observed in the data. The "proximity" vector consists of indicator variables for each well site regardless of whether it had been fractured at the time of the birth. These indicators are equal to 1 if the distance between maternal residence and the given well site is within a short distance (that is, 0 to 1, 1 to 2, or 2 to 3 km in alternative specifications) and 0 otherwise. We then define an indicator, Near_i, that is the result of applying the maximum operator to the full vector for birth i. That is, if there are any wells within the specified radius, then this indicator Near_i will take the value 1 and 0 otherwise. This variable is a practical solution to summarizing the information on distance associated with each of the nearly 8000 wells; specifically, it is a measure of whether there is at least one well in the relevant distance category and it is a key covariate in Eq. 1.

The "timing" vector also has a separate indicator for each well that is equal to 1 if conception occurred after the spud date and 0 otherwise. The idea is that it is implausible that a well could affect infant health before it is spudded. The differences in spud dates across wells, even with relatively small geographic areas, mean that it is possible to include month-year indicators and region-specific time trends to adjust for any underlying time effects.

Having defined these two vectors, we multiply to create a new vector and apply the maximum operator to the product vector. The result is the indicator variable Exposure_{it}, which is equal to 1 for births near any well sites for which the spud date precedes conception and is equal to 0 otherwise. Thus, after adjustment for the full set of covariates described in the preceding paragraphs, the key parameter of interest is $a_{2,}$ which measures whether there are changes in infant health near well sites where hydraulic fracturing started before the conception date.

One reason why birth outcomes might differ in an area before and after fracking is that the population of mothers may change with active fracturing. Previous work has shown, for example, that housing prices can be affected by industrial activity (*12*, *23*, *24*), which could be expected to change the population living nearby over time. One way to deal with this problem is to compare each mother to herself. Hence, we next estimate

$$Y_{it} = a_i + a_1\text{Near}_{it} + a_2\text{Exposure}_{it} + a_3\text{X}'_{it} + a_4\text{County}_{it} + a_5\text{Time}_{it} + a_6\text{Regional\_trend}_{it} + e_{it} \quad (2)$$

which differs from the study of Bamberger and Oswald (*4*) in that it includes a constant term for each mother, a_i. Because the a_i absorbs the effect of any constant or time invariant characteristics (that is, race, education, etc.) of the mother, the vector X'_{it} now includes only time-varying elements of X_{it}. Table S1 reveals that mothers with multiple births are more likely to be married and also more likely to have either high or low levels of education. Hence, although Eq. 2 removes concerns about confounding fracking exposure with other determinants of infant health, it is possible that the effects of exposure to fracking differ in the subpopulation of mothers with more than one child in the data.

Three additional details are worth noting. First, there was no a priori correct way to define "Near" because there is no physical law that determines the distance at which fracking-related activities potentially affect infant health. Consequently, we estimated models that explore the effect of each additional kilometer of distance from a well. These models took the same form as Eq. 1, except that "Near" was replaced with a vector of indicators for whether the mother lived 0 to 1, 1 to 2 km, 2 to 3, …, 10 to 15 km from a well. The omitted distance category was greater than 15 km. A mother's residence can be both 0 to 1 km from one well and 2 to 3 km from another; hence, these categories are not necessarily mutually exclusive. We also calculated 15 "Exposure" variables analogously to the way these indicators were described above; the coefficients associated with these variables test for any changes in infant health in these 15 distance bands around well sites where hydraulic fracturing started before the conception date, relative to the rest of Pennsylvania. We found little evidence of an effect of fracking exposure on infant health at distances greater than 3 km, and this motivated our focus on 0 to 1, 1 to 2, and 2 to 3 km as the definitions of "Near," as well as the use of infants born to mothers living more than 3 km away as the comparison group.

A second issue is that secular trends in infant health outcomes may differ across small geographic areas (that is, because of hospital closings or openings or local economic shocks). For this reason, the subsequent analysis reports result from the estimation of versions of Eqs. 1 and 2 that limit the sample to a 15-km radius around a well site. The advantage of this smaller sample is that mothers living 3 to 15 km away from a well site may be affected by the same economic shocks as those who live within 3 km. In contrast, this assumption seems less likely to be valid for mothers living further away, for example in Philadelphia. In addition, rather than only allowing time trends to vary by region, we also defined a 0.5° latitude × 0.5° longitude grid and controlled for a time trend for each cell in this grid. This alternate specification provides a flexible method to adjust for secular changes in infant health that are unrelated to fracking exposure.

All models were estimated using the REG and XTREG commands in STATA 14.0. The SEs in these and all our models were clustered by mother to allow for correlations between siblings in other determinants of birth outcomes.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/12/e1603021/DC1

table S1. Comparison of mothers by number of births observed in sample.

table S2. Effect of fracturing on infant health (including both inactive and active wells).

table S3. Effect of fracturing on infant health (treatment based on birth date).

table S4. Effect of fracturing on infant health (controlling for latitude/longitude grid*year controls).

table S5. Mothers with <2 well sites spudded within 1 km versus mothers with 2+ well sites spudded within 1 km.

table S6. Effect of fracturing on infant health (logit for low birth weight).

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ATTACHMENT C

STUDY 6

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Shale Gas Development and Infant Health: Evidence from Pennsylvania

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Abstract

This research exploits the introduction of shale gas wells in Pennsylvania in response to growing controversy around the drilling method of hydraulic fracturing. Using de- tailed location data on maternal addresses and GIS coordinates of gas wells, this study examines singleton births to mothers residing close to a shale gas well from 2003–2010 in Pennsylvania. The introduction of drilling increased low birth weight and decreased term birth weight on average among mothers living within 2.5 km of a well compared to mothers living within 2.5 km of a future well. Adverse effects were also detected using measures such as small for gestational age and APGAR scores, while no effects on gestation periods were found. These results are robust to other measures of infant health, many changes in specification and falsification tests. In the intensive margin, an additional well is associated with a 7 percent increase in low birth weight, a 5 gram reduction in term birth weight and a 3 percent increase in premature birth. These findings suggest that shale gas development poses significant risks to human health and have policy implications for regulation of shale gas development.

Keywords

infant health; shale gas development; air pollution; water pollution; low birth weight

[6] To date, there are no estimates in Pennsylvania of how many properties are “split estate”- the condition where surface owners do not own the mineral rights.

[16] I also test whether drilling activity has affected these characteristics directly by changing fertility and/or the composition of families living near shale gas development and I find few economically significant changes.

[17] Johnson and Schoeni (2011) use national data from the US and find that low birth weight increases the probability of dropping out of high school by one-third, lowers labor force participation by 5 percentage points, and reduces earnings by almost 15 percent. More recently, Figlio et al. (2014) use linked birth and schooling records in Florida and find that birth weight has a significant impact on schooling outcomes for twin births.

[24] Only one maternal characteristic shows a significant change with drilling: mothers observed after drilling are more educated than those observed prior to drilling (results not shown). Increased college completions among mothers would potentially improve observed infant health in these communities. However, this does suggest some selection and so I include these and other controls in all the subsequent results.The time frame of interest is during the onset of the Great Recession. It may indicate that the opportunity cost of going to college, or becoming a mother, has reduced and so more educated mothers are having children. Other research has linked recessions to improved infant health outcomes, so it is unlikely to be the driver of impacts reported in the next section (Chay and Greenstone, 2003b; Dehejia and Lleras-Muney, 2004).

The United States (US) holds large unconventional gas reserves in relatively impermeable media such as coal beds, shale, and tight gas sands, which together with Canada account for virtually all commercial shale gas produced in the world (IEA, 2012).[1] New technologies, such as hydraulic fracturing and directional drilling, have made it economically and practically feasible to extract natural gas from these previously inaccessible geological formations.[2] In 2010, unconventional gas production was nearly 60% of total gas production in the US (IEA, 2012). Natural gas from the Marcellus formation, particularly in Pennsylvania, currently accounts for the majority of this production (Rahm et al., 2013).[3] A recent assessment by The Wall Street Journal estimates that over 15 million Americans live within 1 mile of an oil or gas well drilled since 2000 in 11 of the 33 states where drilling is taking place (Gold and McGinty, 2013). With this expansion, it is becoming increasingly common for shale gas development to take place in close proximity to where people live, work and play.

The expansion of shale gas development (SGD) in the US has brought with it a national debate that seemingly lacks a consensus over its economic, environmental, health and social implications. There is growing evidence that shale gas development creates jobs and generates income for local residents in the short run (Allcott and Keniston, 2014; Bartik et al., 2016; Feyrer et al., 2017; Hausman and Kellogg, 2015; Mason et al., 2015). In addition to its economic benefits, many claim that a move to natural gas (and away from petroleum- or coal-based energy) will support U.S. energy independence and national security. Shale gas provides an attractive source of energy because it emits fewer pollutants (e.g., carbon dioxide, sulfur dioxide, nitrogen oxides, carbon monoxide and particulate matter) when burned than coal and other fossil-fuel energy sources per unit of heat produced (Chen et al., 2017). Globally, the shale boom has improved ambient air quality and displaced coal-based electricity, especially for areas with coal-fired power plants (Johnsen et al., 2016). However, these benefits may come with local costs associated with drilling activity in communities where it takes place. These costs may include reduced environmental quality through local air pollution (Colborn et al., 2012; Litovitz et al., 2013; Witter et al., 2013), water contamination (Warner et al., 2012; Olmstead et al., 2013; Hill and Ma, 2017), increased truck traffic (Graham et al., 2015) and health. Concerns over perceived ground water contamination have caused a discount of housing prices to compensate for the risk and an approximately $19 million increase in bottled water purchases in 2010 in response to SGD in Pennsylvania (Muehlenbachs et al., 2015; Wrenn et al., 2016). This is further supported by a recent cost-benefit analysis that found substantial environmental costs associated with health damages from air pollution emitted by SGD totaling $27.2 billion (Loomis and Haefele, 2017).

In utero exposure to air pollution has been linked to adverse birth outcomes, lower educational attainment, labor market outcomes and future health problems (See Currie and

[1]The International Energy Agency (IEA) defines unconventional gas as sources of gas trapped in impermeable rock deep underground.
[2]Hydraulic fracturing (popularly known as “fracking” or “fracing”) stimulates the well using a combination of large quantities of water (“high-volume”), fracturing chemicals (“slick water”) and sand that are injected underground at high pressure. This process fractures the rock and causes the resource to be released.
[3]Pennsylvania experienced very rapid development of shale gas, with 4,272 shale gas wells drilled from 2007–2010 (PADEP, 2010a).

Schmieder (2009); Currie (2009); Currie et al. (2014b) for summaries of this research). In particular, a large literature has linked air pollution (e.g. particulate matter (PM), carbon monoxide (CO), sulfur dioxide ($S0_2$), nitrogen oxide (NO_x)) from coal-fired power plants with low birth weight, premature birth and infant mortality both within the US and in the developing world.[4] With natural gas touted as a transition fuel between coal-based electricity and renewable options, infant health is one way to compare costs across alternative options. While coal is undeniably worse than natural gas with respect to resource extraction and energy generation, concerns regarding emissions associated with shale gas should be studied (Chen et al., 2017).

The impact of shale gas development on health has become the focus of a growing body of literature. To my knowledge, Hill (2012) is the first study to assess the impact of shale gas development on infant health. Concurrent health studies include case studies (Bamberger and Oswald, 2012), health impact assessments (McKenzie et al., 2012), toxicological assessments of specific chemicals (Colborn et al., 2011), self-reported health symptoms (Ferrar et al., 2013) and studies exploiting administrative records such as birth certificates, hospital records or electronic medical records (EMR) to study asthma, pneumonia, fatigue, migraine, sinus effects, and birth outcomes (Hill, 2013; McKenzie et al., 2014; Stacy et al., 2015a; Rasmussen et al., 2016; Casey et al., 2016; Tustin et al., 2017; Currie et al., 2017; Whitworth et al., 2017; Peng et al., 2018).[5] All but one of the infant health studies find a positive association between drilling and poor birth outcomes measured by premature/ preterm birth (PTB) or low birth weight (LBW). Due to a lack of consistency in outcomes, proximity, and exposure metrics used, it is challenging to compare findings across these studies.

To assess the impact of shale gas development on infant health, I build a unique database that contains the longitude and latitude of all shale gas wells, the street address (geocoded) of all new mothers, and data on whether the mother’s address falls within public water service areas. To define a treatment variable, I exploit both the timing of drilling activity (using the “spud date,” or the date the drilling rig begins to drill a well) and the exact locations of well heads relative to residences. I then use as a comparison group mothers who live in proximity to future wells, as designated by well permits. The exact locations of both wells and mothers’ residences allow me to exploit variation in the effect of shale gas drilling within small, relatively homogeneous socio-economic groups, and the timing of the start of drilling allows me to confirm the absence of substantive pre-existing differences. Through this method, I am able to provide robust estimates of the impact of maternal exposure to shale gas development during pregnancy on birth outcomes.

The main results suggest both statistically and economically significant effects on infant health. I find that shale gas development increased the incidence of low birth weight and

[4]See Chay and Greenstone (2003a); Currie and Neidell (2005); Jayachandran (2009); Tanaka (2015); Knittel et al. (2015); Sanders and Stoecker (2015); Clay et al. (2016); Arceo Eva et al. (2016); Yang et al. (2017); Yang and Chou (2017); Severnini (2017); Jha and Muller (2017). For example, Yang et al. (2017) found that after a power plant in PA closed down, low birth weight declined by 15 percent and premature birth by 28 percent due to reductions in PM2.5 and S02.

[5]See Colborn et al. (2011) regarding health effects of fracturing chemicals; see McKenzie et al. (2012) for a review of studies investigating the effects of inhalation exposure; see Vengosh et al. (2014) for a review of the likely effects of water contamination from SGD; see Werner et al. (2015), Stacy (2017), and Balise et al. (2016) for recent reviews of SGD and health related studies.

small for gestational age in the vicinity of a shale gas well by 25 percent and 18 percent, respectively. Furthermore, term birth weight and birth weight were decreased by 49.6 grams (1.5 percent) and 46.6 grams (1.4 percent), on average, respectively and the prevalence of APGAR scores less than 8 increased by 26 percent. Results for premature birth were mixed and sensitive to specification. The difference-indifferences research design, which relies on the common trends assumption, is tested by examining the observable characteristics of the mothers in these two groups before and after development, testing for pretrends in the outcome variables using the sample before drilling, permit dates only, and future wells only, and using a random date to define treatment. The research design is robust to these tests as well as a range of specifications. I examine mobility using the group of mothers with more than one birth and find that there is little evidence of moms moving in response to drilling. I perform a back of the envelope calculation on the costs of these activities using my estimates and the estimated population within 1 mile of drilling from the Wall Street Journal (e.g. 15 million Americans) and estimate that drilling costs more than $230 million per year in the 11 out of 33 gas producing states. This estimate is likely to be a lower bound given that this assessment doesn’t include all states with development and that I use a lower bound estimate of the costs associated with low birth weight.

This paper contributes to the literature using a quasi-experimental design and is a combination of the strengths of both the epidemiologic and economic literature described above. First, I improve upon the epidemiologic literature by employing a difference-in-differences design. In particular, I exploit the exogeneity of drilling conditional on leasing and permitting, which results in statistically homogenous treated and comparison groups. This provides a more stable comparison group than in Currie et al. (2017) that compares to those living within 3–15km. Second, I improve upon the economics literature by using the strengths of the epidemiologic literature by looking at multiple measures of adverse infant health outcomes which may be indicative of different aspects of drilling exposure. Preterm birth is indicative of preterm premature rupture of membranes, which can result from genetics, stress or low socio-economic status (SES) (Goldenberg et al., 2008). Low birth weight and small for gestational age (SGA) are more related to intrauterine growth restriction (IUGR), which is more consistently related to air pollution (Stieb et al., 2012b; Sun et al., 2015; WHO, 2005). Congenital abnormalities indicate exposure to a teratogen during pregnancy. Given the inconsistency in measured outcomes in existing studies, I simultaneously estimate impacts for all outcomes within the same sample and identification strategy. This is particularly useful for policy given the mixed findings in the existing studies and that none of these studies directly test exposure mechanisms. Third, I improve upon the economics literature by thoroughly controlling for predictors of infant health and estimating the extensive and intensive margins of drilling. I include controls for insurance status, WIC, previous risky pregnancy, parity, and smoking status. I also measure heterogeneity across SES subgroups and test whether moms are moving in response to drilling. Importantly, I contribute to the literature by measuring the effect of an additional well on birth outcomes, which is perhaps more relevant to policy-making than simple binary measurements of exposure.

The rest of the paper proceeds as follows: section I presents background and context and section II describes the data. Section III presents graphical evidence and section IV describes the estimation strategy. Sections V and VI presents results and robustness checks. Section VII provides interpretation and discussion of the results. Section VIII concludes.

I Background

I.I A Brief Shale Gas Overview for Pennsylvania

In Pennsylvania, shale gas development involves primarily high-volume hydraulically fractured horizontal wells drilled into the Marcellus Shale and more recently, the Utica Shale. Hydraulic fracturing is a process to stimulate a well that uses water to fracture the rock or shale beneath the ground. On average, in Pennsylvania, it involves injecting approximately 4–8 million gallons of water mixed with sand and fracturing chemicals into the well and using pressure to fracture the shale about 6,500–7,500 ft below the surface (Chen and Carter, 2016). Shale plays are heterogeneous and so the distance drilled and quantity of water required differ across varied geological formations. The entire process of completing a natural gas well takes, on average, 3–9 months to finish: access road and well pad construction occurs for a month (0–4 weeks) prior to the spud date, drilling the well takes about 30 days (vertical drilling for 0–2 weeks and horizontal drilling for 4–8 weeks), preparation for hydraulic fracturing takes 1–2 months, hydraulic fracturing takes about 7 days, flowback occurs for 2–8 weeks and clean up and testing takes about a month before the well goes into production (Casey et al., 2015; Graham et al., 2015). During the first few months, diesel trucks bring in materials required for the drilling process, averaging 1500–2000 truck trips per well completion in Pennsylvania. During the first 30 days after well stimulation, it is estimated that approximately 30–70% of the water used during the drilling process returns to the surface (called flowback) and is collected in ground level water impoundments and then taken to be treated at a waste water facility (Kondash et al., 2017).

Most wells are drilled on private property that has been leased to oil and gas companies. [1]After the land is leased by the mineral owner, a company applies for a permit to drill on that property. The state government approves permits and once a company has a permit, the drilling often commences quickly thereafter. There are many layers of decision-making independent of the mineral owner that determine exactly which leases become permits and which permits become a well. This research uses only those locations that are permitted by the state to reduce selection bias in the estimates that follow.

The identification strategy used in this paper depends on the assumption that drilling is exogenous relative to locations that are permitted but not yet drilled. However, areas that are permitted but not drilled may be different from areas that experience active drilling. For example, areas without active drilling may not have as many property owners willing to lease mineral rights or the industry may prioritize leasing in areas with the most productive shale. Appendix Figure A1 overlays the parcels with leases from Drillinginfo with the strata of shale depth from EIA. For counties where we have lease data, the extent of leasing is densest along the deepest contours and more sparse along the shallower contours, except in the northeastern part of the state such as Bradford County. To examine this further, I linked the lease and depth data to the wells and permits used in these analyses to test whether there are substantial differences.[7] There are no differences in leasing defined by the proportion of acres leased within Census block groups between permitted and drilled wells. The average

Census block group in the data is 40 percent leased for both permitted and drilled locations. In the top 10 drilled counties, this jumps to 60 percent, but is again the same across permitted and drilled locations. Permits that are drilled seem to be explained by shale depth as opposed to some difference in community preference as proxied for by leasing activity.

I.II Shale Gas Development As A Potential Pollution Source

Preliminary evidence indicates that shale gas development may produce waste that could contaminate the air, aquifers, waterways, and ecosystems that surround drilling sites or areas where water treatment facilities treat the waste water from the drilling process. Below I review the current state of the scientific evidence.

I.II.1 Water Pollution—There are a number of mechanisms by which shale gas development might contaminate ground and surface water sources and thereby impact either public or private drinking water. According to a recent assessment by EPA, these mechanisms include: spills of hydraulic fracturing (HF) fluids prior to mixing with large quantities of water or produced water after hydraulic fracturing has taken place, injection of hydraulic fracturing fluids into wells with inadequate mechanical integrity (e.g. faulty well casings), injection of HF fluids directly into groundwater sources, discharge of inadequately treated hydraulic fracturing wastewater to surface water, and disposal or storage of hydraulic fracturing wastewater in unlined pits (EPA, 2016; Osborn et al., 2011; Jackson et al., 2013; Olmstead et al., 2013; Warner et al., 2013).[8] The EPA report identified 1,084 chemicals reported to be used in hydraulic fracturing fluids and 599 chemicals detected in produced water(EPA, 2016). Of the 599 chemicals detected in produced water, only 77 were also reported to be used in hydraulic fracturing fluid– which is not a great match. The report found that chemicals used in HF fluid varied greatly across regions, which limits external validity(EPA, 2016).[9] Elliott et al. (2017) provides a review of these chemicals for reproductive and developmental toxicity.[10]

The lack of reliable information about what chemicals are used leaves the scientific community testing many different chemicals across regions, with little overlap among detected chemicals. Studies of groundwater contamination have primarily used private drinking water wells and assessed proximity to shale gas wells to assess contamination (e.g. within 5 km of gas wells versus larger distances) (Hildenbrand et al., 2016; Osborn et al., 2011; Jackson et al., 2013). Studies have found increases in organics (many naturally occurring such as chlorides, bromides and iodides, arsenic, selenium, manganese, strontium, barium, heavy metals, beryllium), volatile and semivolitile organic compounds (e.g. BTEX, 2-Butanone), diesel range organic compounds, solvents (e.g. methanol, dichloromethane), and methane (Drollette et al., 2015; Hildenbrand et al., 2015, 2016; Yan et al., 2016;

[7]Available upon request.

[8]Scientists face challenges in assessing the potential for contamination due to limited baseline data on water quality, lack of publicly available data regarding the chemicals used in fracturing uid, the sheer number of chemicals use and naturally occurring contaminants returning to the surface in the process of drilling and hydraulic fracturing.

[9]See Chen et al. (2017) for more information about specific chemicals of concern. The EPA Report has a large appendix characterizing each chemical with citations.

[10]Toxicity information was lacking for 781 (76%) chemicals. Of the remaining 240 substances, toxicological studies suggested reproductive toxicity for 103 (43%), developmental toxicity for 95 (40%), and both for 41 (17%). Of these 157 chemicals, 67 had or were proposed for a federal water quality standard or guideline.

Alawattegama et al., 2015; Burton et al., 2016). Some studies have not found any evidence of contamination, leaving whether SGD impacts water quality a hotly debated question (Li et al., 2016). One study assessing groundwater-sourced public water systems' water quality found that SGD wells were associated with an increase in SGD-related chemicals for wells drilled within 1 km of the groundwater source (Hill and Ma, 2017).

Surface water impacts are more likely to be associated with the handling of shale gas waste. Waste water treatment and discharge is associated with elevated levels of barium, strontium, bromides, chlorides, benzene, and total dissolved solids exceeding the maximum contaminant level for drinking water (Olmstead et al., 2013; Vengosh et al., 2014; Hladik et al., 2014; Lester et al., 2015; Ferrar et al., 2013). Treated produced water (containing naturally occurring bromide and iodide) are potential sources of toxic disinfection byproducts (DBPs): iodinated trihalomethanes (THMs) and brominated haloacetonitriles (HANs) in surface water (Parker et al., 2014).[11] Endocrine disrupting chemicals measured in surface water near waste effluent in Colorado and West Virginia are of concern for reproductive health (Kassotis et al., 2015).

I.II.2 Air Pollution—Despite less attention in the media, air pollution is gaining more recent attention by researchers. All stages of shale gas development have the potential to produce hazardous air pollution emissions (Kargbo et al., 2010; Schmidt, 2011). Air pollution has become a more immediate concern following studies in Colorado that discovered higher levels of volatile organic compounds (VOCs), methane and other hydrocarbons near drilling sites (Colborn et al., 2012; Pétron et al., 2012). Other emissions associated with combustion include particulate matter, poly-cyclic aromatic hydrocarbons, sulfur oxides and nitrogen oxides (Colborn et al., 2012). More recent studies have also assessed the air pollution contribution of the many truck trips necessary to build and fracture a well (McCawley, 2017; Goodman et al., 2016).

Studies of air pollution in Pennsylvania are suggestive of increased emissions associated with shale gas development, but have produced inconsistent results. For example, the Pennsylvania Department of Environmental Protection (PA DEP) has conducted three short-term (1 week) air pollution studies in three regions of the state but found little evidence of air pollution concentrations that would likely trigger air-related health issues associated with Marcellus Shale drilling activities (PADEP, 2010b, 2011b, a). But the air emissions inventory for the unconventional natural gas industry, starting in 2011, indicates modest emissions of CO, NO_x, PM_{10}, SO_x and VOCs (PADEP, 2013a).[12] These results were verified by a recent RAND study that used the PA DEP data and other sources to estimate the emissions from shale gas in Pennsylvania (Litovitz et al., 2013). The most significant pollutants, according to the authors, were NO_x and VOCs, which were equivalent to or larger than some of the largest single emitters in the state and the low-end estimates of nitrogen oxide emissions were 20–40 times higher than the level that would be defined as a "major" emissions source. During the same time period, due to the conversion of electricity

[11]This is also true for groundwater public drinking water systems that treat their water prior to distribution.

[12]According to this emissions inventory, shale gas wells emit carbon monoxide, NOx, PM10, PM2.5, SOx, volatile organic compounds (VOCs), Benzene, ethylbenzene, formaldehyde, hexane, toulene, xylene, trimethylbenzene, CO2, and Methane (Author's calculations of wells drilled 2011–2016).

from coal to natural gas in the state, the overall pollution for all the criteria pollutants measured decreased substantially and more than outweighed the new pollution related to shale gas development. These data, however, indicate a more nuanced picture of air emissions from drilling activities and show that shale gas development is now a significant source of air pollution in rural counties with few other point-sources of pollution. For example, the 2,600 tons and 2,440 tons of shale-related NO_x emitted in Bradford County and Susquehanna County, respectively in 2011 make up one-third of the statewide shale-related NO_x of 16,500 tons (PADEP, 2013b). These levels surpass the singlelargest industrial source of NO_x pollution in the 11-county northeast region, a coal-fired power plant in Northampton County that emitted 2,000 tons in 2011 (Legere, 2013).

As mentioned above, Pennsylvania DEP began requiring companies drilling Marcellus shale gas wells to report annual estimates of air emission to an inventory starting in 2011. In Table 1, I estimate the intensive margin of the number of wells in a zip code on the annual tons of each pollutant aggregated to that zip code from 2011 to 2015. I also estimate tertiles of wells to capture intensity. Each additional well contributes an average of 0.5 tons of CO, 2 tons of NO_x, 0.07 tons of $PM_{2.5}$, 0.03 tons of SO_x, and 0.17 tons of VOCs per year. The average zip code in 2011 experienced 14 tons of CO, 41 tons of NO_x, 1.4 tons of $PM_{2.5}$, 0.5 tons of SO_x, and 8 tons of VOCs. In the subset of wells that were spudded prior to 2011, the average well produced 2 tons of CO, 4.7 tons of NO_x, 0.14 tons of $PM_{2.5}$, 0.04 tons of SO_x, and 0.63 tons of VOCs in 2011. The top tertile (14–213 wells) of zip codes experience an average of 28 tons of carbon monoxide (CO), 90 tons of NO_x, 2.6 tons of $PM_{2.5}$, 1.8 tons of SO_x, and 9 tons of volatile organic compounds (VOC) per year. Babies exposed to shale gas development within 10 km face an average of 24 wells (max of 240) in 2010 and is fairly similar to the tertiles used in Table 1 Although there isn't a direct way to measure the contribution of these emissions to ambient air quality, they do represent a modest and potentially significant amount of emissions for these rural areas.

Of interest is whether wells continue to produce emissions after drilling and entering into production. To test this, I estimate the amount of reported emissions per year per pollutant using years since spud date as the regressors for all wells reported in the emissions inventory from 2011–2015 (Appendix Table A1). For the most part, emissions are largest for the year of the spud date and the first year after drilling occurred, but emissions continue for most pollutants out to years 4 or 5. Due to this evidence, I estimate models using wells drilled from 2006–2010 and determine exposure by wells drilled prior to birth as opposed to restricting just to drilling activity during gestation.

I.III Pollution and Health Literature

Stillerman et al. (2008) review the epidemiological literature and find associations between low birth weight and maternal exposures to PM, SO_2, CO, NO_x, VOCs and ozone. Most of the studies cited looked at these pollutants in isolation, but with shale gas development mothers are likely exposed to many at the same time and there is little research that examines any compounding effects.[13] All of the air pollutants emitted by shale gas

[13]See Currie et al. (2009); Shah and Balkhair (2011); Stieb et al. (2012a); Glinianaia et al. (2004); Sram et al. (2005) for other reviews of past literature related to air pollution and birth outcomes.

development described above have been associated with adverse birth outcomes (see Online Appendix for more detail). Unfortunately, many of the epidemiological studies do not take into account socio-economic status and so the observed relationships could reflect unobserved factors that may be correlated with pollution and infant health outcomes (i.e. urban areas). The epidemiological literature relating water pollution to reproductive health is more limited (see Quansah et al. (2015) and Nieuwenhuijsen et al. (2013) for recent reviews).

There is a growing literature within health economics that addresses the most common air pollutants associated with SGD described above utilizing quasi-experimental designs and rich controls for potential confounders to identify the infant health effects of ambient air pollution. See Currie et al. (2014b) for a review of the economics literature on short and long term impacts of early life exposure to pollution. For example, Currie and Walker (2011) estimate that reductions in air pollution from E-Z Pass result in reductions of low birth weight (LBW) between 8.5–11.3 percent and Zahran et al. (2012) utilize the natural experiment of benzene content in gasoline from 1996 to 1999 in the US and found exposure to benzene reduces birth weight by 16.5 g and increases the odds of a very low birth weight event by a multiplicative factor. Lavaine and Neidell (2013) use the natural experiment of a strike that affected oil refineries in France to explore the temporary reductions in SO_2 and find that the reductions increased birth weight by 75 grams, on average (2.3 percent increase) and reduced low birth weight by 2 percentage points for residences within 8 km of the air pollution monitor.

With natural gas touted as a transition fuel between coal-based electricity and renewable options, infant health is one way to compare costs across alternative options. To date, even within the epidemiological literature, studies of the effects of living near coal mining (underground or mountain top) on birth outcomes are extremely limited. All three studies focus on WV: one found an increased risk of low birth weight (16 percent increase in most intensive areas) and one study found an increased risk of congenital anomalies with mountain top removal mining associated with worse outcomes, but was later refuted by the third study when the authors controlled for hospital of birth (Ahern et al., 2011b, a; Lamm et al., 2015). See Hendryx (2015) and Boyles et al. (2017) for systematic reviews of the public health literature. However, recent papers in the economics literature have exploited plant openings and closings or being downwind from a plant to identify the causal impact of coal-fired power plants on infant health and have found adverse birth outcomes: a 5 percent reduction in continuous birth weight as the grid transitioned from nuclear to coal in Tennessee (Severnini, 2017), a 6 percent increase in low birth weight for infants 20 miles downwind of a power plant (Yang et al., 2017), 15 percent decreased risk for low birth weight once the plant closed (Yang and Chou, 2017), and 3,500 infant deaths per year as of 1962 associated with the expansion of the power grid between 1938 and 1962 (Clay et al., 2016). A recent paper focused on storage of coal at power plant locations found that a 10 percent increase in PM2.5 from coal storage increased infant mortality rates by 6.6 percent (Jha and Muller, 2017).

I.III.1 SGD and Health Literature—Most of the studies to date that address potential health impacts of shale gas development measure pollutants at drilling sites or in drilling fluids and then identify the health implications based upon expected exposure to these chemicals (e.g. toxicological assessment). For example, Colborn et al. (2011) find that more than 75% of the chemicals could affect the skin, eyes, and other sensory organs, and the respiratory and gastrointestinal systems. Chronic exposure is particularly concerning because approximately 40–50% could affect the brain/nervous system, immune and cardiovascular systems, and the kidneys; 37% could affect the endocrine system; and 25% could cause cancer and mutations. These may have long-term health effects that are not immediately expressed after a well is completed. Recent studies have found increased hospitalizations for cardiac conditions (Jemielita et al., 2015), increased risk of three types of asthma measures (Rasmussen et al., 2016), increased risk of hospitalization for pneumonia (Peng et al., 2018), and increased prevalence of fatigue, migraine and sinus effects for residents living near development (Tustin et al., 2017).

A growing body of literature has attempted to address the potential reproductive health effects of shale gas development. All of these studies are retrospective analyses of birth certificate records or electronic medical record data and focus on proximity to maternal residences as the definition of "exposure." In Colorado, McKenzie et al. (2014) find an increased risk of congenital heart defects with the highest quartile of exposure compared with the absence of any gas wells within a 10-mile radius of the maternal residence. They also found a reduction in premature birth and low birth weight for the highest quartile of exposure. Hill (2013) finds an increase in the latter two measures of around 30 percent for oil, natural gas and coalbed methane wells. Using a similar research design in Texas, Whitworth et al. (2017) finds an increase in premature birth of 14 percent and an increase in fetal death upwards of 50 percent. Using a case-control analysis, Whitworth et al. (2199) find a 20 percent increase and 15 percent increase in preterm birth for any wells and producing wells within 0.5 miles of the maternal residence, respectively.

Focusing on the three studies in Pennsylvania, Stacy et al. (2015a) study three counties in Southwestern Pennsylvania from 2007–2010 and Casey et al. (2016) study two hospitals in the Geisinger Health System from 2009–2013.[14] Currie et al. (2017) study birth records from Pennsylvania from 2004–2013. Stacy et al. (2015a) use inverse distance weighted number of wells within 10 miles of the maternal residence and create quartiles to define exposure (compare 4th to 1st quartiles; omitting mothers with no wells within 10 miles). Casey et al. (2016) create an"activity index" and use quartiles of the index (compare 4th (average 124 wells, median 8) to 1st quartile (average 6 wells, median 0), but include those with no wells within 20 km). [15]Currie et al. (2017) utilize a difference-in-difference study design comparing close (e.g. 0–1, 1–2, 2–3km) versus further away (e.g. all PA or 3–15km) in Pennsylvania using county fixed effects. Stacy et al. (2015a) find a reduction in birth weight and an increase in small for gestational age (SGA) of 34 percent. Casey et al. (2016) find an increase in premature birth that ranges from 40 to 90 percent and an increase in the prevalence of risky pregnancies. Currie et al. (2017) find a 25 percent increase in low birth weight for the 0–1km group. The 2–3km buffer suggests a 16 percent increase in low birth

[14]Both of these study populations are contained within the population studied in this paper.
[15]According to the authors, the index does not distinguish between pregnant women living near several producing wells versus well pads under development.

weight. The 1–2km buffer is not as consistent or statistically precise as the 0–1 or 2–3km buffers. Other measures studied include continuous birth weight and a health index. Currie et al. (2017) further estimate their models using maternal fixed effects but these models are not statistically significant, nor are they consistent with all of their primary findings.

In the discussion section (Section VII), I compare and contrast my results with those cited above and also provide discussion of interpretation.

II Data

My analysis is based upon a data set acquired from the Pennsylvania Department of Environmental Protection (PA DEP) that contains GIS information for all of the wells drilled in the state of Pennsylvania since 2000 and define whether it is a Marcellus shale well. For the analysis that follows, the spud date (date when the drilling rig begins drilling the well) is used as the temporal identification of treatment. In total, the analysis uses 2,459 natural gas wells spudded between 2006 and 2010. In addition to the existing gas well data, this study also makes use of the permit data on the PA DEP website. This allows for the identification of permits that do not become a well during the sample time frame; approximately 40 percent of permits do not become a well (author calculation from PA DEP data). This information is used to define a potential control group for those infants born to residences close to existing gas wells. The assumption is that these residences are a potential counterfactual group: those who have the potential to live close to a gas well in the future, but have not yet had a well drilled as of the timing of the data collection. Figure 1 shows drilled and permitted wells through 2010 along the strata of shale depth. For the most part, wells that are drilled are clustered along the deepest shale strata and permitting is more random.

My second source of data comes from restricted-access vital statistics natality and mortality data from Pennsylvania for the years 2003 to 2010. The restricted-access version of these birth certificate records contain residential addresses geocoded to latitude and longitude and unique identifiers for the mother, father and infant. This precision is essential to my identification strategy because the consequences of drilling are highly localized. To construct the analysis data set, I combine the spatially identified wells and maternal residences and calculate proximity to the nearest wells.

The vital statistics contain important maternal characteristics such as race, education, age, marital status, WIC status, insurance type, previous risky pregnancy and whether the mother smoked during her pregnancy. In the empirical analyses that follow, I control explicitly for these, as well as month of birth, year of birth, the interaction, and gender of the child.[1] I exclude multiple births in all analyses because plural births are more likely to have poor reproductive health independent of exposures to environmental pollution.

I focus on low birth weight (LBW), premature birth and term birth weight (TBW) as the primary outcomes of interest. Low birth weight, defined as birth weight less than 2500 grams, and premature birth, defined as gestation length less than 37 weeks, are commonly used as key indicators of infant health and have been shown to predict adult health and well-being.[1] I also present the continuous measure of term birth weight, defined as birth weight for infants who reach full term at 37 weeks gestation, to study whether there is an average effect on the birth weight distribution as opposed to these more extreme health outcomes. Other birth outcomes that I examine include the continuous measure of birth weight, gestation (measured in weeks), small for gestational age (SGA; defined as 10th percentile of weight distribution for the gestational week of birth), an indicator for whether the APGAR score is less than 8 to predict an increased need for respiratory support, congenital anomalies, an infant health index and infant mortality (death in the first year).[18]

Table 2 provides summary statistics for the universe of births in Pennsylvania from 20032010. The first column reports characteristics of all births and the second column reports average characteristics of births for mothers' residences within 2.5 km of where a shale gas well has been drilled or will be drilled. The localized data I use in this analysis is actually quite similar to the characteristics of the rest of the state. Mothers who live close to shale gas development are less likely to be African American and Hispanic, slightly better off in terms of health outcomes, younger, better educated and more likely to be married at the time of birth compared with the state average. The mothers in the analysis sample are also more likely to smoke than the average for the state. Columns (3) and (4) provide summary statistics for the primary difference-in-difference (DD) analysis sample; the sample is restricted to those mothers' residences within 2.5 km of a gas well or permit and I compare residences before and after drilling. Most of the statistically significant differences between these two samples are arguably not very economically important. Mothers with infants born after drilling are less likely to be over the age of 35, more likely to receive WIC, and more likely to receive Medicaid, on average, likely to do with the shale gas boom coinciding with the Great Recession. However, Table 3 suggests no changes in these economic variables after shale gas development.[19]

III Graphical Evidence

If living close to a drilled well has a negative impact on infant health, we should see average prevalence of low birth weight for mother's residences in close proximity to wells increase subsequent to when drilling begins. Moreover, we should observe larger impacts for homes closest to drilling activity (e.g. dose response). Figure 2 shows the low birth weight (LBW) and premature birth gradients of distance to closest well before and after drilling. LBW prevalence is on average higher for those residences close to drilled wells, compared with those who are close to permitted wells. The primary effect appears to be within 2.5 km but

[18]Small for gestational age (SGA) is used to determine the immediate health care needs of the infant and is used increasingly to predict long-term adverse health outcomes and potential exposure to environmental pollution (Callaghan and Dietz, 2010). This paper uses the World Health Organization weight percentiles calculator (WHO, 2011). Another potential measure of reproductive health is the 5 minute American Pediatric Gross Assessment Record (APGAR) score. The physician rates the infant a 0, 1, or 2 on each of 5 dimensions (heart rate, breathing effort, muscle tone, reex initiability, and color), and then sum the scores, giving an APGAR score of 0–10, where 10 is best. This discrete measure is highly correlated (when the score is low) with the need for respiration support at birth (Almond et al., 2005). Most of these outcomes has been previously examined in both the epidemiological and economics literature (e.g., Currie and Walker (2011)). Following Currie et al. (2014a), I also construct a single standardized measure to address examining multiple outcomes and multiple hypothesis tests. I first convert each birth measure so that an increase is "adverse" and then standardize the measure to a mean of zero and standard deviation of 1. I then construct the summary measure by taking the mean over the standardized outcomes, weighting them equally.

[19] An examination of fertility over time suggests a consistent number of births within 2.5 km of the well head. Muehlenbachs et al. (2015) do not end any changes in neighborhood composition using Census data at the tract level from 2000–2012 in Pennsylvania.

persists out to almost 5 km (consistent with regression results). In contrast, we do not see a clear trend in premature birth over distance (regresion results are mixed depending on extensive or intensive measures).

In Figure 3, I explore pre-trends in these two outcomes across treatment (e.g. drilled wells) and control (e.g. permitted wells) groups, which addresses the validity of my difference-in-difference design. Prior to drilling in 2008, trends appear parallel and indicate a diverging trend once drilling begins.

A primary threat to my identification strategy is that the population of mothers may change in response to drilling. One way to test this is to graph the gradient in observable maternal characteristics. In Figure 4, I graph this gradient out to 20 km.[20] The gradient is very similar within 5 km of the nearest gas well before and after drilling. If anything, moms after drilling may be more college educated, which is consistent with my regression results. However, the characteristics change meaningfully beyond 5 km, and moms who live more than 5 km from a gas well before or after drilling are more likely to be college educated, less likely to have their birth paid for by Medicaid, less likely to participate in WIC and less likely to smoke. This suggests selection into living very close to drilling/future drilling and that those who live closer may have lower SES than those who live 15–20 km away. This could drive adverse outcomes related to living very close to drilling, which is why I use permitted locations that are similarly close to mothers' residences since these groups are more homogeneous and statistically similar.

IV Empirical Strategy

I exploit the variation over time and across space in the introduction of shale gas wells in Pennsylvania during 2003–2010. Combining gas well data and vital statistics allows the comparison of infant health outcomes of those living near a gas well and those living there before drilling began. Rather than compare aggregated areas, I know specific locations where shale gas drilling has taken place and the dates of when drilling began. The specific location data allow me to compare reproductive health within very small areas in which mothers are likely to be more homogeneous in observable and unobservable characteristics than in aggregate comparisons.

Relying on cross-sectional variation alone, however, would be problematic if mother characteristics vary within the small radius of interest that are unobservable to the researcher. If, for example, the location of gas drilling occurs where the neighborhoods are already economically distressed, then the variation in health outcomes may reflect socio-economic status, as opposed to living in close proximity to shale gas development. I therefore examine localized reproductive health outcomes before and after shale gas development exploiting permitted but not-yet-drilled wells as a comparison. I use 2.5 km (approximately 1.5 miles) as the primary distance of interest for the main specifications that

[20] This is the largest distance used as a treated group in related studies. McKenzie et al. (2014) use 10 miles, Stacy et al. (2015b) use 10 miles, Casey et al. (2016) uses 20km, Whitworth et al. (2017) use 10 miles and Currie et al. (2017) use 15 km.

follow due to my graphical analyses as well as due to the precision of the effect at this distance for robustness checks.[21]

My primary model is a difference-in-difference model – in which mothers living within 2.5 km from a shale gas well or permit before drilling are used as a control for those exposed after drilling began – to estimate the impact of exposure to shale gas development on birth outcomes. Thus, the counterfactual change in infant health for mother's residences close to a shale gas well is estimated using births prior to drilling at the same distance from the well bore location or permitted location (e.g. those permits that become a well by 2011 are treated differently than those permits that are not drilled by 2011). These models take the following form:

$$Outcome_{it} = \beta_1[Well \leq X]_{it} + \beta_2[Post]_{it} + \beta_3[Well \leq X]_{it} * [Post]_{it} + \beta_4 X_{it} + \gamma_t + \chi_c + \epsilon_{it} \quad (1)$$

where $Outcome_{it}$ is either low birth weight, prematurity and other measures of reproductive health for each infant i born in month-year t. $[Well \leq X]_{it}$ is either an indicator for any gas well or the number of gas wells within X km of the mother's residence. $[Post]_{it}$ is an indicator for whether the birth occurs after the spud date of the nearest well of the maternal residence. The estimated impact of shale gas development on infant health is given by the coefficient β_3 and is the difference-indifferences estimator comparing before and after drilling holding the distance X km fixed for wells, future wells and permits.[22] The vector X_{ict} contains mother and child characteristics including indicators for whether the mother is African American, Hispanic, four mother education categories (less than high school (left out category), high school, some college, and college or more), mother age categories (teen mom (left out category), 19–24, 25–34 and 35+), indicators for smoking during pregnancy, an indicator for receipt of Women, Infants, and Children (WIC), three health care payment method categories (Medicaid, private insurance, and self-pay), mother's marital status, parity, previous risky pregnancy and an indicator for sex of the child. Indicators for missing data for each of these variables were also included. γ_t are indicators for the year, month and year*month to allow for systematic trends. χ_c are indicators for each mother's county of residence. Standard errors are clustered at the county.[23]

[21]In Appendix Tables A3 and A4, I report different proximities to gas wells for the definition of treatment and show that for distances up to 5 km, the results are fairly robust.

[22]By including permitted wells not drilled, this estimation strategy becomes more than just a pre-post analysis. This identification strategy assumes that infants born within a similar distance to a permit that is a potential future

[23]Due to the localized nature of this estimation strategy, there is little variation within zip codes to allow for zip code fixed effects. Models with zip code fixed effects are qualitatively similar but less precisely estimated. Results available upon request.

V Results

V.I Differences in Characteristics of Mothers Close to a Well

To test the validity of my research design, I estimate equation (1) and use the difference-indifference estimator to see if there are any changes in mother characteristics after drilling began well would face similar ex ante conditions as those born close to a permit that did become a well during the period I have gas well data for (2003–2011). Infants born to mothers who reside close to potential wells are likely to be the most similar comparison group when it comes to family, geological formation and community characteristics. The decision for which permits become a well is arguably exogenous to the families in these locations. This should account for both observable characteristics, as well as unobservable characteristics, such as economic factors that promote gas drilling in a community and the unobserved geology of the shale underneath these communities. I test these assumptions and do not find any observable differences in the characteristics of mothers who live close to a future well versus a permitted and not yet drilled well.

(e.g. replace birth outcomes with indicators for maternal characteristics). In Table 3: Panel B, I do not find any indication that maternal characteristics are changing in response to shale gas development. In Appendix Table A2, I show that there are no statistically significant differences in maternal characteristics for any potential proximities (e.g. 2km-3.5km).

V.II The Impact of Shale Gas Development on Birth Outcomes

Table 4 shows the results from estimating (equation 1) on low birth weight, term birth weight and premature birth. Distance to a well, including future and permitted, is held fixed at 2.5 km for these models. Each coefficient represents an estimate of β_3 – the difference-in-difference estimator – from a separate regression. Columns (1), (3) and (5) show a model that controls only for month and year of birth, month*year and county fixed effects. Adding controls for observable characteristics of the mother should only reduce the sampling variance while leaving the coefficient estimates qualitatively unchanged. Columns (2), (4) and (6) add maternal characteristics and show that controlling for maternal characteristics has controlling for maternal characteristics has little effecton the estimated coefficients for low birth weight and term birth weight. I find a statistically significant increase in low birth weight of 1.36 percentage points and a reduction in term birth weight of 49.58 grams, on average. I do not find any statistically significant effect for premature birth. Thus, mothers who give birth after drilling are more likely to have reduced weight babies, but they come to term. This difference indicates an overall increase in low birth weight of 24 percent (base of 5.7 percent) and a decrease in term birth weight of 1.5 percent (base of 3416 grams), on average.[25]

The results are qualitatively similar when I estimate equation (1) for other distances up to 5 km from a gas well or permit (See Appendix Table A3). As the buffer of exposure expands, the point estimates become smaller, indicating a dose response relationship, with effects dissipating beyond 3.5 km. The advantage of using permits as the counterfactual is that I can

[25]Overall prevalence is calculated as follows: 0.0136/0.057=23.9 percent low birth weight and 49.6/3416 = 1.5 percent reduction in term birth weight.

look at only residences that are going to be very close to gas wells at some point in the observable future, which should account for the economic benefits for households receiving lease royalties from the industry.[26]

Table 5 presents estimates of (equation 1) for changes in birth weight, 5 minute APGAR scores less than 8, gestation (weeks), small for gestational age (SGA), congenital anomaly, and an index for infant health due to having multiple outcomes of interest.[27] As before, each column presents estimates from a separate regression, comparing outcomes before and after drilling at 2.5 km from a well head or permit. I present results with maternal controls due to there being little appreciable difference for the models without these controls (results available upon request). Looking across all reproductive health measures, these estimates are consistent with shale gas development being detrimental to infant health. The introduction of shale gas development reduced birth weight by 46.6 grams (1.4 percent reduction), which is consistent with the findings for term birth weight. Five minute APGAR scores were also affected by drilling; drilling increased scores less than 8 by 2.51 percentage points or an overall increase of 26 percent. Small for gestational age (SGA), a strong indicator of intrauterine growth restriction (IUGR), increased by 1.81 percentage points or an increase of 18 percent from the mean. Perhaps surprisingly, given that low birth weight is often correlated with premature birth, gestation shows no difference with the introduction of SGD (similar to the findings for premature birth). I do not find any impact on congenital anomaly, despite McKenzie et al. (2014) finding an increase in Colorado. A drilled shale gas well has a small and statistically significant effect on the summary index, increasing the probability of an adverse reproductive health outcome by 0.026 standard deviations. This result is consistent with the finding that living within 1 mile of an operating toxic plant increased the probability of a poor health outcome by 0.016–0.017 standard deviations (Currie et al., 2014a).

V.III Well Density

Given the finding that the introduction of shale gas development adversely affects birth outcomes in a binary or extensive margin framework, it follows to consider how the density of well development might impact the main outcomes of interest. For the primary sample used in Table 4, the average number of wells drilled at 2.5 km prior to birth is 0.6 wells (s.d. 2.12) with a range of 0 to 35. When limited to those who have at least one well drilled within 2.5 km prior to birth (the “treatment group”) the average increases to 2.98 wells (s.d. 2.62). In Table 6, I present findings that regress infant health on well density. I find that for each additional shale gas well drilled prior to birth within 2.5 km, low birth weight increases by 0.3 percentage points and term birth weight is reduced by 5 grams. Unlike the previous

[26]Permitted wells must have already gone through the leasing process and households that lease their mineral rights will have received signing bonuses previously. These benefits can only reach an approximate 3km buffer where horizontal drilling can reach minerals and would result in royalties. At very close proximities (e.g. < 1km), I see some indication that birth outcomes are improved by drilling. There is a large and growing literature that suggests positive income shocks can have a positive effect on birth outcomes (Almond et al., 2011; Hoynes et al., 2015) and so this ending would be consistent with that hypothesis. Royalties may mitigate the risks of close exposure.

[27]Following Currie et al. (2014a), I address the issue of precision using a summary index measure of infant health. I first convert each birth measure so that an increase is “adverse” and then standardize the measure to a mean of zero and standard deviation of 1. I then construct the summary measure by taking the mean over the standardized outcomes, weighting them equally.

specification, I also find that each additional well increases premature birth by a similar 0.3 percentage points.[28]

As before, these findings are consistent across proximity buffers from 2 to 5 km, as shown in Appendix Table A4, and also show some degree of dose response for low birth weight and premature birth. At 2 km, estimates for LBW and preterm birth are about 0.4 percentage points and drop to about 0.02 percentage points at 5 km. The relationship for term birth weight shows less of a dose response, but peaks at 2.5 km with 5 grams and drops to < 1 gram at 5 km.

VI Robustness Checks and Heterogeneity of Impacts

VI.I Heterogeneity by Maternal Characteristics

The economics literature measuring health effects of pollution considers avoidance behavior to be an important factor to explore (Currie (2009); Neidell (2004); Currie et al. (2014b)). If families engage in avoidance behavior (e.g. move, use water purification or purchase bottled water (Wrenn et al., 2016), avoid going outside during drilling), then the health effects measured could be a lower bound. To assess this, the literature tests heterogeneity across characteristics to determine whether there are differential impacts by SES (Currie et al., 2013b; Sanders and Stoecker, 2015). This would not reflect a biological difference, but would provide evidence for or against maternal behavioral responses to shale gas. Table 7 contains estimates of heterogeneity for three primary measures of infant health: low birth weight, term birth weight, and premature birth (each reported as a separate panel). Each column and coefficient represents an estimate of β_3 in equation (1) from a separate regression to explore whether the effects of exposure to shale gas drilling are the same for different subgroups of the population. For the most part, the results for low birth weight and term birth weight indicate that there is not much heterogeneity of impacts across demographic groups–shale gas development has detrimental impacts on all subgroups. However, high school dropouts and moms on Medicaid do experience larger impacts with increases in low birth weight of about 4 percentage points and college educated mothers have slightly smaller impacts of about 1 percentage point.[29] No subgroups have statistically significant impacts for prematurity and similar to before, the signs of the coefficients are not consistently positive or negative.

In Hill (2012), I also report estimates of maternal mobility for the sample of mothers who have multiple singleton births and those who have ever resided within 2.5 km of a well or future well during 2003–2010. I found that moms may be moving in response to shale gas development (an increase of 2.2. percentage points), but it was not statistically significant. Despite some potential increased mobility of these mothers, I found that the results are

[28]I also estimate models using tertiles of wells and find that the top tertile (> 3 wells) has a similar sized effect as the extensive margin results for low birth weight and term birth weight, however, the top tertile increases premature birth by 2 percentage points, in contrast to the null finding in the extensive margin results.

[29]The pre-drilling mean for these three groups are substantially different from the overall average. The percentchanges relative to the mean for both HS dropouts and Medicaid reect a 50 percent increase, while the effect for college educated moms reects a 25 percent increase, which is the same as the main effect. I tested the differences between these and the main results and only the results for Medicaid are statistically different [pvalue=0.01]

qualitatively similar for those who stay as those who move and indicate that the main results are not driven by maternal mobility.

VI.II Sensitivity Analyses

Additional robustness checks were performed to make sure the main specifications are robust to different counterfactual groups, additional controls and subsets of counties associated with production and drilling. These results are reported in Appendix Table A6. First, I limit the sample to mothers who were born in Pennsylvania to test whether migration from out of state is driving the main findings. The results are very similar for the 83 percent of moms who were born in PA.[30]

Next, I report the estimates using the 10 most drilled counties and the 10 most producing counties (these are not the same) and find similar results indicating that it is not just drilling or production driving these findings.[31]

Another difference-in-difference model commonly used in the environmental health literature is to compare observed health close to a pollution source versus slightly further away. For example, (Currie and Walker, 2011) compared mothers within 2 km of a toll plaza to mothers who are 2–10 km from a toll plaza, before and after the adoption of E-Z Pass in Pennsylvania and New Jersey. In Hill (2012), I compared residences close to a well (a range of proximities as before of 2–3.5km) and residences a little further away (5, 10 and 15km), before and after drilling.[32] The results are consistent with the main findings for low birth weight and term birth weight, but as described in the graphical evidence section, there may be selection into proximity and so this in not a preferred specification.

VI.III Falsification Tests

My analysis shows little evidence of any preexisting differences in communities located close to drilled wells relative to communities close to permits or future wells. It is theoretically possible that the increase in low birth weight after drilling is driven by differential trends in fertility or migration post-drilling among mothers who do not have multiple births during the sample. I investigate this possibility by estimating equation (1) using permit dates to define exposure, instead of spud dates. I also create a placebo test using a random date for the closest well. In these specifications, I find no evidence of a

[30]This does not perfectly address this question since migration can also occur within PA.

[31]Other robustness checks were reported in Hill (2012). First, I showed the results for restricting the sample to infants born within 2 years (before and after) of the spud date for the closest well. This specfcation is designed to address any possible concerns about unequal prior and post observation periods for each location or concerns about unobserved and differential sorting in the mothers living close to drilled versus permitted wells. The point estimates are somewhat smaller, but qualitatively similar to the estimates in Tables 4 and 5. Next I showed the results using the sample of births from 2008 to 2010, when most of the shale gas development took place during the sample frame. This point estimate is slightly larger for low birth weight (LBW) indicating a 1.89 percentage point increase. Finally, I reported the results from adding the continuous distance to the closest well, as well as the number of wells drilled within 5 km of the maternal residence. Again, the point estimates are very similar to those reported in Tables 4 and 5 and suggest most of the effect is driven by proximity to the closest well.

[32]In Hill (2012), I used up to 15 km as the comparison group and reported it as a lower-bound estimate; shale gas development increases the overall prevalence of low birth weight by 12.5 percent and reduces term birth weight by 0.6 percent, on average. Depending on the scale of shale gas development, it is possible that other aspects of drilling activity will inuence infant health within 15 km of a well and could explain these smaller estimates. For example,communities with shale gas development are exposed to increased truck trafic, pipelines, water storage, compressor stations and general increased localized economic activity. These community level effects are less likely to inuence the estimates in the main results of the paper that use permitted/future wells as the comparison group.

spurious effect (Table 8). I also run models on future wells and repeat the well density models using number of future wells. These models are also consistent with no impact and are consistent with the conclusion that shale gas development has an adverse impact on birth outcomes.

VII Discussion

My results suggest that shale gas development can have adverse effects on the health of people living nearby, namely that of prenatal infants. For the extensive margin, babies born of mothers who lived within 2.5 km of at least one gas well during pregnancy experienced adverse birth outcomes. I find supportive evidence that these effects persist out to 3.5 km of a mother's address and are consistent across multiple specifications. For the intensive margin, or estimating the impact of well density, I find that each additional well drilled within 2.5 km of the mother's residence increases low birth weight and premature birth by 0.4 percentage points and reduces term birth weight by 5 grams.

These results are reasonable for three reasons. First, most areas with shale gas development in Pennsylvania are rural areas with relatively low prevalence of low birth weight (5.7 percent) compared to the state average of 7 percent (for singleton births only).[33] The studies cited in this paper that assess low birth weight impacts of air emissions from other sources (e.g. EZ-Pass, mountain-top coal mining) report baseline average prevalence of low birth weight of 9 or more percent (Currie and Walker, 2011; Ahern et al., 2011b) and therefore mechanically lower relative effect sizes. However, the average birth weight in this population is almost identical to the state average and is 1.5 percent relative to the mean, which is not large, and is very similar or smaller than the average impact on birth weight of exposure to air emissions in other studies (Severnini, 2017; Lavaine and Neidell, 2013; Yang and Chou, 2017). Second, most of the existing literature has studied the effects of air pollution on infant health on a pollutant-by-pollutant basis. In this case, I am identifying the health effects of exposure to the disamenity itself, which according to the air emissions inventory emits a wide variety of pollutants. Some, such as NO_x, are much higher than the largest pre-drilling emitter in the region.[34] Each of these contaminants have been separately associated with the birth outcomes measured in this paper, while SGD increases exposure to all of these during active drilling and production. Thus, it is not surprising that my estimates are larger than some of those found in the literature, especially those that are studying one pollutant. Finally, these results are smaller than or similar in magnitude to the existing literature studying the infant health impacts of shale gas development (Stacy et al., 2015b; Casey et al., 2016; Currie et al., 2017; Whitworth et al., 2017, 2199).

My study builds upon the existing literature measuring the infant health impacts of shale gas development. Due to inconsistency in measures used across existing studies, it is challenging to compare and interpret measured impacts. My results are consistent with Currie et al. (2017) for low birth weight and Stacy et al. (2015a) for small for gestational age. While I do

[33]Using the pre-drilling mean of low birth weight for the analysis sample, the effect size is 24 percent relative to the mean, whereas the effect size is 19 percent relative to the state average.

[34]As mentioned in the background section of the paper, the largest industrial source of NOx in the 11-county region is a power plant that produces 2,000 tons per year. Shale wells in 2011 produced 16,000 tons of NOx in aggregate.

not find an impact on premature birth in the extensive margin, my intensive margin results indicate that premature birth may be impacted, especially at the highest tertile of exposure. This most closely relates to the inverse distance weighted quartile measures used in the epidemiologic literature and is consistent with Casey et al. (2016) and Whitworth et al. (2017). Although exact mechanisms are difficult to ascertain with the data currently available, the increase in small for gestational age and low birth weight in the extensive margin without a symmetric increase in premature birth indicates that infants born to mothers exposed to any drilling are coming to full term, but are small, as would be the case where drilling persistently increases local air or water pollution. Whereas, preterm labor may be induced by air pollution or stress at higher intensities of drilling and therefore explain the symmetric intensive margin impacts on preterm birth and low birth weight (Dole et al., 2003; Stieb et al., 2012b; Sun et al., 2015).

These results suggest that requiring air and water pollution monitoring of drilling sites could assist researchers and public health officials in efforts to ascertain exposure pathways for residents living nearby and inform policies to mitigate any risks that are likely to be very localized. In 2011, PA DEP began requiring the shale gas industry to report emissions of these pollutants into an emissions inventory so that policy makers can better address these exposures in the future.

The effects of gas drilling are larger for lower SES children. There is prior evidence that in some cases this is explained by the fact that lower SES women take fewer measures to avoid pollution. I do not, however, detect heterogeneous responses as measured by mothers moving. As previously mentioned, early shocks to a child’s health can persist for many years, hence if poorer families are unable to mitigate the risks of drilling activity their children’s health is likely to suffer, which is reflected in literature that finds pollution to be one potential mechanism by which SES affects health (Neidell, 2004). Given the wealth of studies that identify a causal link between birth weights and long-run outcomes, these impacts are likely to persist throughout these children’s lives.

VII.I Cost Estimates

While the economic benefits and costs of shale gas development are quantifiable, the public health benefits and costs might be more difficult to assess. This paper provides evidence that maternal exposure within at least 1.5 miles of SGD is detrimental to fetal development. Due to shale gas development occurring only recently in Pennsylvania, the number of infants observed close to existing wells is quite small relative to other more populated areas with SGD. This translates to a cost of $4.1 million.[35] As a back-of-the envelope estimate, there are more than 2.8 million American women of reproductive age with a well within a mile of their homes (Gold and McGinty, 2013; Howden and Meyer, 2010).[36] Using the current fertility rate of 64 per 1,000 women in this age group nationally (Martin et al., 2012), there

[35]Combining hospital costs attributable to low birth weight ($15,100 in additional hospital costs)(Russell et al., 2007), estimates for special education services ($5,200)(Chaikind and Corman, 1991; Augenblick et al., 2007) and decreased earnings ($76,800)(Currie et al., 2013a), an arguably conservative estimate is $96,500 in added cost for each low birth weight child. This figure excludes medical bills after the first year, parental lost earnings and other costs and is, hence, a lower bound estimate of costs.

[36]Using The Wall Street Journal estimate that over 15 million Americans live within 1 mile of an oil or gas welldrilled since 2000, and using a rough estimate that half of those people are women and forty percent of them are ages 18–44.

are over 170,000 pregnant women living within 1 mile of a well in these states. Using the estimates in this paper as a benchmark, oil and gas development in these communities could amount to over 2,000 additional low birth weight infants each year which amounts to a cost of more than $230 million per year in these 11 states.

VIII Conclusions

My study seeks to understand and quantify the impacts of shale gas development on infant health. As a first step, I assembled a unique data set with the latitude and longitude of new mothers' residences and the locations of shale gas wells and permits in Pennsylvania. I examine the impacts of living in close proximity to shale gas development on low birth weight, term birth weight and other measures of infant health.

These results suggest that shale gas wells are associated with reduced average birth weight among infants born to mothers living within a 2.5 km radius from a shale gas well; this implies a monetized cost of $4.1 million. The impacts associated with shale gas studied in this paper are large but not implausible given the estimates found in the literature for air pollution impacts on low birth weight and term birth weight. The strength of this approach is in exploiting a natural experiment that controls for unobservable characteristics and the results are robust across a variety of specifications, providing evidence on the credibility of the research design.

It is clear from these results that policies intended to mitigate the risks of shale gas development can have significant health benefits. I find detectable effects of shale gas development on low birth weight and term birth weight more than 3.5 km from the well head (more than 2 miles or over 11,000 ft). This finding is of significant independent interest and an important contribution of this paper.

Current required set back distances (distance between well head and nearby residences, hospitals and schools) range from 300 ft to 800 ft across the 33 states where shale gas development is taking place. With detectable infant health effects up to 2 miles away, these set back distances may be deemed insufficient to protect human health. The impacts of shale gas development estimated in this paper are independent of drinking water source and suggest that the mechanism by which shale gas development adversely affects reproductive health is through the pathway of air pollution. This finding also adds impetus for regulators to increase regulations that reduce air pollution emissions from drilling operations and for industry actors to increase voluntary action to reduce air pollution emissions.

Since I have focused on only the infant health effects of shale gas development, the total health effects of drilling exposure are likely to be much greater. Further research on the longer term health impacts of shale gas development on all members of our society –as well as the probable mechanisms and how best to mitigate them– is warranted.

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Appendices

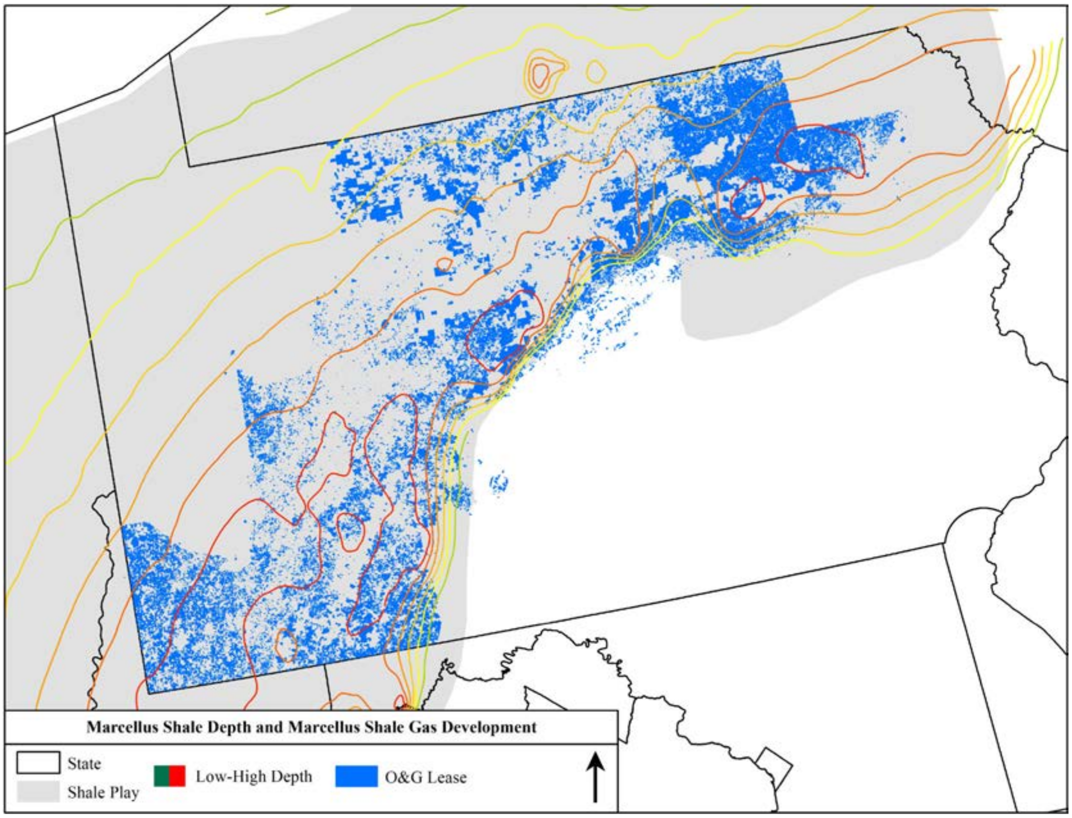

Figure A1:
Map of Leasing through 2010

Table A1:

Emissions from Shale Gas Wells First 5 Years after Spud Date

	(1) co	(2) nox	(3) pm10	(4) pm25	(5) sox	(6) voc
Year of Spud	2.188***	7.938***	0.282***	0.259***	0.107***	0.585***
	(0.0517)	(0.136)	(0.00614)	(0.00537)	(0.00538)	(0.0463)
One Year Since Spud	2.241***	6.709***	0.225***	0.202***	0.0656***	1.008***
	(0.0532)	(0.140)	(0.00632)	(0.00552)	(0.00558)	(0.0473)
Two Years Since Spud	0.595***	1.351***	0.0612***	0.0550***	0.00860	0.719***
	(0.0577)	(0.152)	(0.00685)	(0.00596)	(0.00607)	(0.0501)
Three Years Since Spud	0.378***	0.661***	0.0289***	0.0256***	0.00985	0.427***
	(0.0603)	(0.158)	(0.00715)	(0.00622)	(0.00628)	(0.0523)
Four Years Since Spud	0.321***	0.438**	0.0213**	0.0172**	0.00334	0.502***
	(0.0737)	(0.193)	(0.00874)	(0.00760)	(0.00765)	(0.0648)
Five Years Since Spud	0.178*	0.250	0.0107	0.00882	0.00101	0.731***
	(0.100)	(0.264)	(0.0119)	(0.0104)	(0.0104)	(0.0892)
Observations	13,650	13,650	13,610	13,555	13,472	14,073

	(1) co	(2) nox	(3) pm10	(4) pm25	(5) sox	(6) voc
R-squared	0.215	0.299	0.204	0.218	0.038	0.067
Dep. Var Mean	1.242	3.805	0.136	0.123	0.0436	0.675

Table A2:

Differences in characteristics for analysis sample using DD estimator by Distance

	(1) Teen Mom	(2) Dropout	(3) Black	(4) Smoked	(5) WIC	(6) Medicaid	(7) Born PA	(8) Moved
Within 2km * post-drilling	0.00464	−0.00150	0.00181	−0.00366	−0.0195	−0.0288	−0.0198	−0.00125
	(0.00704)	(0.00927)	(0.00457)	(0.0254)	(0.0276)	(0.0273)	(0.0133)	(0.0124)
Observations	14,131	14,131	14,131	14,131	14,026	14,131	14,131	14,060
R-squared	0.015	0.046	0.022	0.031	0.072	0.098	0.025	0.043
Within 2.5 km * post-drilling	0.000550	−0.0132	0.00343	0.00277	−0.00501	−0.0204	−0.0222	0.0191
	(0.00666)	(0.0118)	(0.00308)	(0.0196)	(0.0246)	(0.0282)	(0.0163)	(0.0131)
Observations	21646	21646	21646	21646	21469	21646	21646	21511
R-squared	0.012	0.039	0.016	0.026	0.061	0.078	0.020	0.042
Within 3km * post-drilling	−0.00351	−0.0206	0.00443	−0.0210	−0.0221	−0.0426	−0.0209	0.0159
	(0.0108)	(0.0193)	(0.00550)	(0.0234)	(0.0304)	(0.0371)	(0.0139)	(0.0123)
Observations	28,910	28,910	28,910	28,910	28,655	28,910	28,910	28,741
R-squared	0.010	0.032	0.016	0.025	0.061	0.073	0.017	0.041
Within 3.5km * post-drilling	−0.0140	−0.0258	−0.000432	−0.0234	−0.0451	−0.0451	−0.0160	0.0120
	(0.0108)	(0.0217)	(0.00694)	(0.0266)	(0.0349)	(0.0419)	(0.0173)	(0.0112)
Observations	36,447	36,447	36,447	36,447	36,100	36,447	36,447	36,228
R-squared	0.009	0.029	0.015	0.024	0.057	0.069	0.015	0.040

Notes: See Table 3 for specification details.

Significance:

* p<0.10,

** p<0.05,

*** p<0.01.

Table A3:

The Effect of Shale Gas Development on Infant Health by Distance

	(1) *d* < 2 km	(2) *d* < 2:5 km	(3) *d* < 3 km	(4) *d* < 3:5 km	(5) *d* < 4 km	(6) *d* < 4:5 km	(7) *d* < 5 km
Panel A: Low Birth Weight							
Well in ‘d’ km * post-drilling	0.0127**	0.0136**	0.0115**	0.00912**	0.00533	0.00288	0.00194
	(0.00512)	(0.00511)	(0.00510)	(0.00391)	(0.00406)	(0.00415)	(0.00428)
Observations	14,113	21,610	28,865	36,393	44,690	52,325	59,369
R-squared	0.023	0.021	0.019	0.019	0.018	0.018	0.017
Pre-drilling Mean	0.0584	0.0571	0.0579	0.0579	0.0576	0.0574	0.0575
Panel B: Term Birth Weight							
Well in ‘d’ km * post-drilling	−38.05*	−49.58***	−30.84**	−29.69**	−15.34	−10.25	−7.311
	(21.49)	(14.04)	(14.20)	(12.59)	(9.781)	(11.56)	(9.457)
Observations	13028	19978	26637	33572	40,277	47,105	53,391
R-squared	0.077	0.075	0.078	0.077	0.078	0.076	0.075
Pre-drilling Mean	3415	3416	3415	3412	3412	3415	3415
Panel C: Premature							
Well in ‘d’ km * post-drilling	−0.00962**	0.000354	0.00460	−0.00184	−0.000704	0.000242	0.00273
	(0.00403)	(0.00664)	(0.00455)	(0.00483)	(0.00564)	(0.00503)	(0.00446)
Observations	13,843	21,189	28,309	35,661	43,741	51,139	57,981
R-squared	0.017	0.012	0.010	0.010	0.009	0.009	0.008
Pre-drilling Mean	0.0802	0.0785	0.0791	0.0791	0.0782	0.0783	0.0786

Notes: See Table 4 for specification details.

Significance:

* p<0.10,

** p<0.05,

*** p<0.01.

Table A4:

Impact of Number of Wells by Proximity

	(1) *d* < 2 km	(2) *d* < 2:5 km	(3) *d* < 3 km	(4) *d* < 3:5 km	(5) *d* < 4 km	(6) *d* < 4:5 km	(7) *d* < 5 km
Panel A: Low Birth Weight							
Wells in ‘d‘ km * post-drilling	0.00410*	0.00306***	0.00232***	0.00122**	0.000266	0.000194	0.000209
	(0.00231)	(0.000931)	(0.000758)	(0.000509)	(0.000433)	(0.000302)	(0.000260)

	(1) *d* < 2 km	(2) *d* < 2:5 km	(3) *d* < 3 km	(4) *d* < 3:5 km	(5) *d* < 4 km	(6) *d* < 4:5 km	(7) *d* < 5 km
Observations	14,049	21,524	28,756	36,241	44,442	51,994	58,976
R-squared	0.023	0.021	0.020	0.019	0.018	0.018	0.017
Pre-drilling Mean	0.0583	0.0570	0.0578	0.0578	0.0575	0.0573	0.0575
Panel B: Term Birth Weight							
Wells in 'd' km * post-drilling	−3.857	−5.386***	−4.716***	−3.152***	−2.429***	−1.438**	−0.930**
	(2.609)	(1.632)	(1.331)	(0.818)	(0.644)	(0.570)	(0.415)
Observations	12,694	19,463	25,969	32,692	40,067	46,822	53,049
R-squared	0.080	0.076	0.078	0.077	0.079	0.076	0.075
Pre-drilling Mean	3415	3416	3415	3412	3412	3415	3415
Panel C: Premature							
Wells in 'd' km * post-drilling	0.00366*	0.00257**	0.00212**	0.000889	0.000281	0.000235	0.000406
	(0.00210)	(0.00123)	(0.000889)	(0.000718)	(0.000602)	(0.000398)	(0.000331)
Observations	13,784	21,109	28,206	35,519	43,506	50,825	57,606
R-squared	0.017	0.011	0.010	0.010	0.009	0.008	0.008
Pre-drilling Mean	0.0803	0.0785	0.0790	0.0789	0.0781	0.0781	0.0786

Notes: See Table 6 for specification details.

Significance:

* p<0.10,

** p<0.05,

*** p<0.01.

Table A5:

Robustness Check: Future Number of Wells by Proximity

	(1) *d* < 2 km	(2) *d* < 2.5 km	(3) *d* < 3 km	(4) *d* < 3.5 km
Panel A: Low Birth Weight				
Wells in 'd' km * future	−0.000223	−0.000133	8.19e-05	6.12e-06
	(0.000449)	(0.000341)	(0.000172)	(0.000139)
Observations	14,049	21,524	28,756	36,241
R-squared	0.023	0.021	0.020	0.019
Panel B: Term Birth Weight				
Wells in 'd' km * future	0.977	0.318	0.410	0.730**
	(1.342)	(0.588)	(0.359)	(0.272)
Observations	12,694	19,463	25,969	32,692

	(1) *d* < 2 km	(2) *d* < 2.5 km	(3) *d* < 3 km	(4) *d* < 3.5 km
R-squared	0.080	0.076	0.078	0.077
Panel C: Premature				
Wells in 'd' km * future	0.000394	0.000172	0.000352	0.000290
	(0.000412)	(0.000476)	(0.000273)	(0.000227)
Observations	13,784	21,109	28,206	35,519
R-squared	0.017	0.011	0.010	0.010

Notes: See Table 6 for specification details. Instead of existing wells, this table looks at future wells.

Significance:

* p<0.10,

** p<0.05,

*** p<0.01.

Table A6:

Robustness Checks

	(1) Low Birth Weight	(2) Term Birth Weight	(3) Premature Birth
Panel A: Mom Born in Pennsylvania			
Within 2.5 km * post	0.0128***	−50.87***	−0.00523
	(0.00466)	(15.99)	(0.00645)
Observations	17,491	15,814	17,155
R-squared	0.022	0.081	0.012
Pre-drilling Mean	0.0576	3415	0.0791
Panel B: Top 10 Major Production Counties			
Within 2.5 km * post	0.0160*	−44.52***	−0.00303
	(0.00726)	(12.03)	(0.0104)
Observations	15,052	13,627	14,789
R-squared	0.025	0.081	0.017
Pre-drilling Mean	0.0573	3415	0.0790
Panel C: Top 10 Major Drilling Counties			
Within 2.5 km * post	0.0175**	−46.66***	0.000296
	(0.00576)	(12.36)	(0.00978)
Observations	13,208	11,951	12,957
R-squared	0.024	0.076	0.016
Pre-drilling Mean	0.0559	3423	0.0783

Notes: Each coefficient is from a different regression. The sample is limited to singleton births, the sample with a well/ permit within 2.5 km and to the panel headings listed. All regressions include indicators for month and year of birth, month*year, residence county indicators, an indicator for drilling before birth (defined by closest well), an indicator for residence within 2.5 km of a well or future well and the interaction of interest of Within 2.5km*post-drilling. Maternal characteristics include mother black, mother Hispanic, mother education (hs, some college, college), mother age (19–24,25–34, 35+), female child, WIC, smoking during pregnancy, marital status and payment type (private insurance, medicaid, self-pay, other). Indicators for missing data for these variables are also included. Standard errors are in parentheses and clustered at the mother's residence county.

Significance:

* p<0.10,

** p<0.05,

*** p<0.01.

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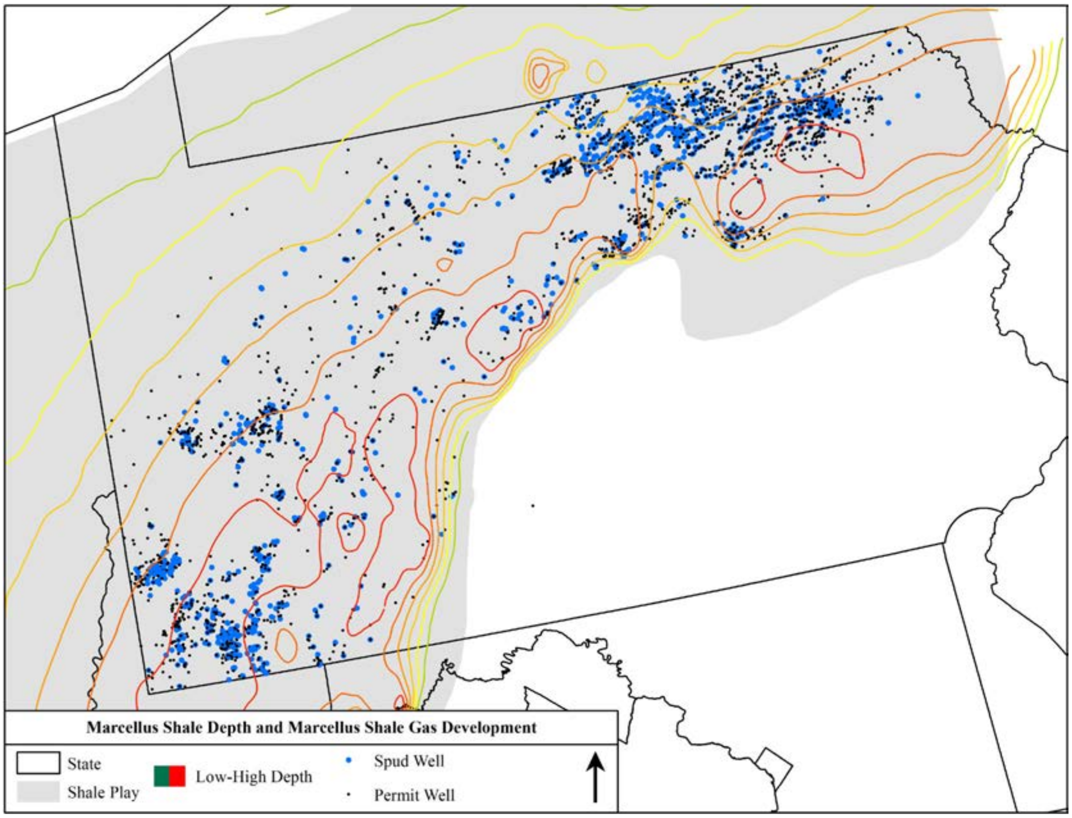
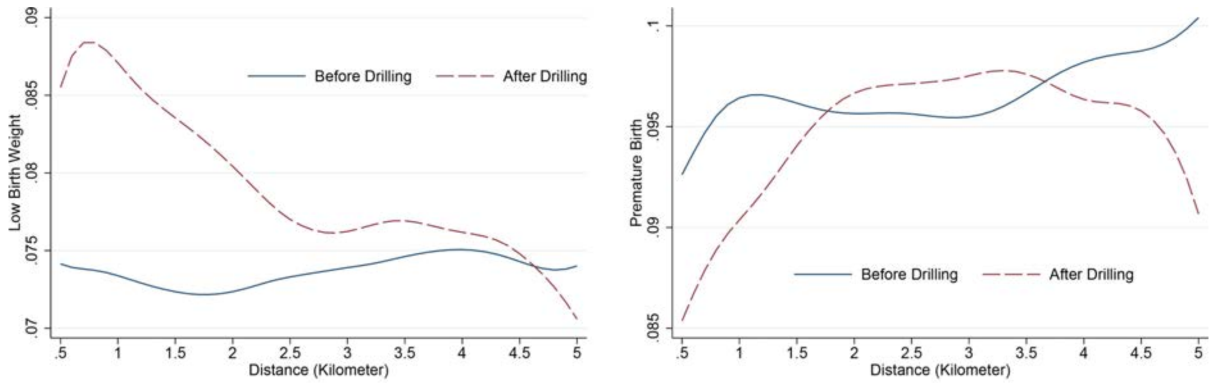


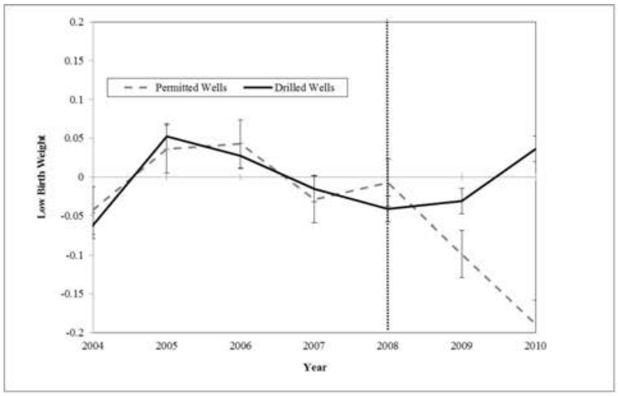
Figure 1:
Map of Shale Gas Development and Permitting through 2010



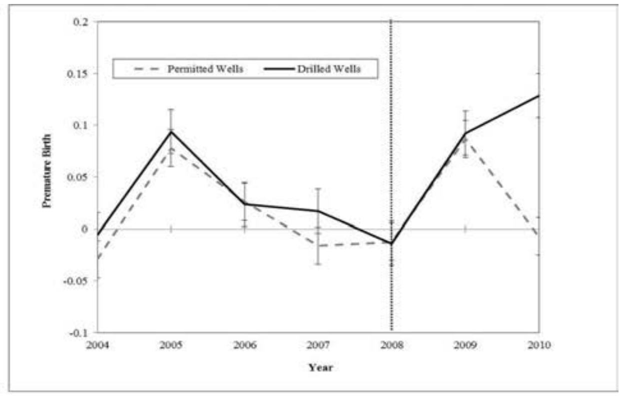
Low Birth Weight Premature Birth

Figure 2:

Distance Gradients of Infant Health by Nearest Well Results from a local polynomial regressions of low birth weight on distance from closest well's future/current location or on days before/after spud date. Observations within 5 km of a well.



Low Birth Weight



Premature Birth

Figure 3:

Time Trends of Infant Health Within 2.5 km of Drilled and Permitted Wells Results are from a regression with an interaction term for drilled well * year including county, birth month and year fixed effects. Observations are the main difference-in-differences sample or those mothers within 2.5 km of a drilled well or permitted well.

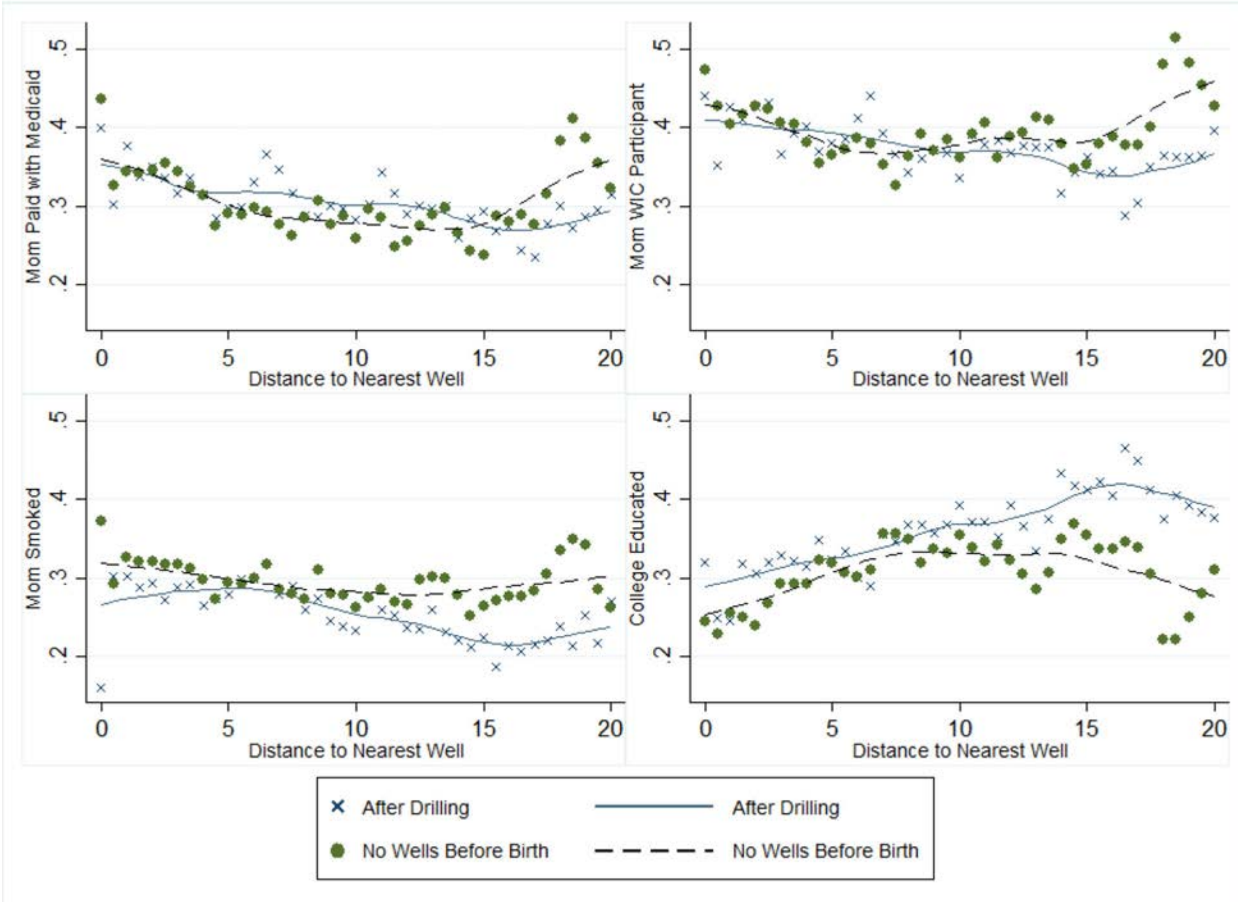


Figure 4:

Distance Gradients of Maternal Characteristics by Nearest Well Distance bins are 0.5 km, smoothed using “lpoly” (degree 0, bandwidth 15).

Table 1:

Pollution Per Well and Tertiles Aggregated to Zip Code 2011–2015

	(1) CO	(2) CO	(3) NO_x	(4) NO_x	(5) $PM_2.5$	(6) $PM_2.5$	(7) SO_x	(8) SO_x	(9) VOC	(10) VOC
# wells	0.526***		2.048***		0.0639***		0.0325***		0.172***	
	(0.0567)		(0.171)		(0.00543)		(0.00500)		(0.0597)	
3–5 wells		3.271		13.28		0.395		0.514**		1.074
		(2.928)		(9.060)		(0.289)		(0.256)		(3.042)
6–13 wells		13.30***		45.02***		1.472***		1.271***		3.835
		(3.305)		(10.23)		(0.326)		(0.289)		(3.434)
14–213 wells		27.47***		89.83***		2.630***		1.777***		9.023**
		(3.934)		(12.17)		(0.388)		(0.344)		(4.087)
log prod	0.552***	0.443**	1.806***	1.627***	0.0633***	0.0598***	0.0336**	0.0241	0.281	0.247
	(0.193)	(0.202)	(0.580)	(0.626)	(0.0185)	(0.0200)	(0.0170)	(0.0177)	(0.203)	(0.210)
Observations	1,172	1,172	1,172	1,172	1,172	1,172	1,172	1,172	1,172	1,172
R-squared	0.697	0.688	0.730	0.707	0.724	0.699	0.500	0.494	0.651	0.650
Dep. Var Mean	15.35	15.35	45.85	45.85	1.482	1.482	0.507	0.507	8.742	8.742

Notes: Data are from the PA DEP Air Emissions Inventory for Unconventional Natural Gas Operations 2011–2015. Units are tons/year. Emissions are aggregated to zip code-year. Regressions include year and zip code fixed effects. First column for each pollutant is number of reported wells in that zip code-year. Second column provides tertile estimates.

Significance:

*p<0.10,

**p<0.05,

***p<0.01.

Table 2:

Summary Statistics by Sample

	All Births	Residences within 2.5 km of well			T-Stat
		Total	Before	After	for difference
Characteristics of birth					
Birth weight (grams)	3321	3340	3343.23	3310.30	2.70 **
Term birth weight (grams)	3407	3415	3418.39	3383.15	3.30 ***
Gestation in weeks	38.77	38.76	38.76	38.71	1.33
Premature	0.08	0.08	0.076	0.077	−0.09
Low birth weight (LBW)	0.07	0.06	0.055	0.063	−1.52
Small for gestational age (SGA)	0.11	0.10	0.098	0.106	−1.25
APGAR 5 minute	8.81	8.89	8.886	8.885	0.07
Female	0.49	0.49	0.485	0.495	−0.95
Mother's Characteristics					
Drop Out	0.164	0.113	0.112	0.118	−0.88
High School	0.270	0.296	0.297	0.288	0.93
Some college	0.260	0.299	0.299	0.293	0.64
College plus	0.298	0.290	0.289	0.299	−1.07
Teen Mom	0.057	0.048	0.047	0.049	−0.34
Mom Aged 19–24	0.265	0.268	0.267	0.274	−0.65
Mom Aged 25–34	0.527	0.547	0.545	0.559	−1.31
Mom Aged 35 and older	0.150	0.137	0.140	0.117	3.03 **
Mom Black	0.156	0.025	0.025	0.024	0.15
Mom Hispanic	0.092	0.011	0.011	0.010	0.57
Married at time of birth	0.575	0.632	0.633	0.626	0.71
Mom Smoked While Pregnant	0.227	0.299	0.299	0.300	−0.13
Received WIC	0.385	0.398	0.395	0.427	−2.94 **
Medicaid	0.272	0.326	0.320	0.376	−5.45 ***
Private Insurance	0.576	0.567	0.569	0.549	1.84
Wells within 2.5 km					
# of wells before birth	0.000	0.333	0.000	2.89	−19.30 ***
# of wells during gestation	0.000	0.188	0.000	1.714	−93.13 ***
Observations	1098884	21610	19246	2364	

Notes: The samples described here include only singleton births.

Significance:

*p<0.10,

**p<0.05,

***p<0.01.

Table 3:

Post- Drilling Differences in Average Characteristics of Mothers Close to Wells

	(1) Teen Mom	(2) Dropout	(3) Black	(4) Smoked	(5) WIC	(6) Medicaid	(7) Born PA	(8) Moved
	Differences in characteristics for analysis sample using DD estimator							
Within 2.5 km * post-drilling	0.000550	−0.0132	0.00343	0.00277	−0.00501	−0.0204	−0.0222	0.0191
	(0.00666)	(0.0118)	(0.00308)	(0.0196)	(0.0246)	(0.0282)	(0.0163)	(0.0131)
Observations	21646	21646	21646	21646	21469	21646	21646	21511
R^2	0.012	0.039	0.016	0.026	0.061	0.078	0.020	0.042
Pre-drilling Mean	0.0496	0.117	0.0243	0.307	0.404	0.323	0.815	0.0756

Notes: Each coefficient is from a different regression. Pre-drilling (post-drilling) refers to births that occur before (after) the spud date of the closest well. Robust standard errors are clustered at the mother's residence county. All regressions include indicators for month and year of birth, birth*year and residence county fixed effects.

Significance:

* p<0.10,

** p<0.05,

*** p<0.01.

Table 4:

Impact of Well Location on Birth Outcomes

	(1) Low Birth	(2) Weight	(3) Term Birth	(4) Weight	(5) Premature	(6)
Within 2.5 km *post-drilling	0.0144**	0.0136**	™47.82***	™49.58***	0.00118	0.000354
	(0.00537)	(0.00511)	(15.12)	(14.04)	(0.00597)	(0.00664)
Observations	21610	21610	19978	19978	21,189	21,189
R-squared	0.008	0.021	0.013	0.075	0.008	0.012
Pre-drilling Mean	0.057	0.057	3416	3416	0.079	0.079
Maternal Characteristics	No	Yes	No	Yes	No	Yes

Notes: Each coefficient is from a different regression. The sample is limited to singleton births and to the sample with a well/permit within 2.5 km. All regressions include indicators for month and year of birth, month*year, residence county indicators, an indicator for drilling before birth (defined by closest well), an indicator for residence within 2.5 km of a well or future well and the interaction of interest of Within 2.5km*post-drilling. Maternal characteristics include mother black, mother Hispanic, mother education (hs, some college, college), mother age (19–24,25–34, 35+), female child, WIC, smoking during pregnancy, marital status and payment type (private insurance, medicaid, selfpay, other). Indicators for missing data

Significance:

* $p < 0.10$,

** $p < 0.05$,

*** $p < 0.01$.

Table 5:

Difference-in-Difference Estimates of the Effect of Drilling on Alternative Health Measures

	(1) Birth Weight	(2) APGAR < 8	(3) Gestation	(4) SGA	(5) Congenital Anomaly	(6) Summary Index	(7)
Within 2.5 km * post-drilling	−47.02***	0.0251**	−0.0143	0.0181**	−0.00193	0.0264**	
	(12.16)	(0.0101)	(0.0664)	(0.00764)	(0.00189)	(0.0101)	
Observations	21,583	21646	21,631	21524	21,646	21646	
R-squared	0.061	0.029	0.020	0.040	0.008	0.045	
Pre-drilling Mean	3340	0.104	38.74	0.0993	0.00562	−0.0372	

Notes: Each coefficient is from a different regression. See Table 4 for details about included covariates.

Significance:

*p<0.10,

**p<0.05,

***p<0.01.

Table 6:

Impact of Well Density on Birth Outcomes

	(1)	(2)	(3)	(4)	(5)	(6)
	Low Birth Weight		**Term Birth Weight**		**Premature**	
Wells within 2.5 km *post	0.00308***	0.00306***	™4.864***	™5.386***	0.00266**	0.00257**
	(0.000868)	(0.000931)	(1.783)	(1.632)	(0.00121)	(0.00123)
Observations	21610	21610	19978	19978	21,189	21,189
R^2	0.009	0.021	0.013	0.076	0.008	0.011
Pre-drilling Mean	0.057	0.057	3416	3416	0.079	0.079
Maternal Characteristics	No	Yes	No	Yes	No	Yes

Notes: Each coefficient is from a different regression. The sample is limited to singleton births and to having a well or permit within 2.5 km. All regressions include an indicator for drilling before birth (defined by closest well), number of wells within 2.5km (including future wells) and the interaction of interest: number of wells within 2.5km *post-drilling. See Table 4 for details about other included covariates.

Significance:

* $p<0.10$,

** $p<0.05$,

*** $p<0.01$.

Table 7:

Shale Gas Development on Maternal Subgroups

	(1) High School dropout	(2) Smoker	(3) Nonsmoker	(4) Medicaid	(5) WIC	(6) College
Panel A: Low Birth Weight						
Within 2.5 km *post	0.0432	0.0186	0.0122**	0.0413***	0.0138**	0.0105
	(0.0268)	(0.0132)	(0.00470)	(0.0120)	(0.00645)	(0.00995)
Observations	2,434	6,465	15,145	7,047	8,541	6,260
R-squared	0.072	0.034	0.018	0.029	0.024	0.029
Pre-drilling Mean	0.0847	0.0830	0.0456	0.0747	0.064	0.0414
Panel B: Term Birth Weight						
Within 2.5 km *post	−42.09	−56.15	−51.36**	−62.97*	−38.30	−49.61*
	(41.26)	(37.10)	(19.04)	(36.70)	(29.02)	(28.45)
Observations	2,191	5,773	13,763	6,375	7,748	5,699
R-squared	0.131	0.064	0.042	0.077	0.076	0.055
Pre-drilling Mean	3305	3272	3479	3325	3349	3494
Panel C: Premature						
Within 2.5 km *post	0.0181	−0.00393	−0.000441	−0.00579	−0.00160	0.000744
	(0.0233)	(0.00950)	(0.00753)	(0.0136)	(0.0142)	(0.0134)
Observations	2,409	6,338	14,851	6,973	8,418	6,122
R-squared	0.070	0.026	0.015	0.027	0.021	0.030
Pre-drilling Mean	0.0896	0.0867	0.0749	0.0859	0.0782	0.0713

Notes: Each coefficient is from a different regression. See Table 4 for details about included covariates.

Significance:

*p<0.10,

**p<0.05,

***p<0.01.

Table 8:

Falsification Tests on Impact of Well Location

	(1)	(2)	(3)	(4)	(5)	(6)
	Permit Date			Random date		
	Low Birth Weight	Term Birth Weight	Premature	Low Birth Weight	Term Birth Weight	Premature
Within 2.5 km *post	−0.000106	−5.03	−0.00149	0.00103	−1.152	−0.00654
	(0.00682)	(12.382)	(0.00897)	(0.00303)	(11.5)	(.00789)
Sample Size	19246	17795	18854	21610	19978	21204
R^2	0.009	0.013	0.009	0.021	0.075	0.012

Notes: See Table 4 for included covariates. Each panel is a separate regression. All regressions include controls for maternal characteristics and time trends and county fixed effects. Columns (1)- (3) use permit date to define “treatment” and the coefficient reported is the interaction between an indicator for whether the permit was within 2.5 km from the mother’s residence and whether the birth occurred after (post) the permit date. Columns (4)-(6) use a random date to define post birth.

Significance:

*p<0.10,

**p<0.05,

***p<0.01.

ATTACHMENT C

STUDY 7

PLOS | ONE

RESEARCH ARTICLE

Setback distances for unconventional oil and gas development: Delphi study results

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Abstract

Emerging evidence indicates that proximity to unconventional oil and gas development (UOGD) is associated with health outcomes. There is intense debate about ªHow close is too close?º for maintaining public health and safety. The goal of this Delphi study was to elicit expert consensus on appropriate setback distances for UOGD from human activity. Three rounds were used to identify and seek consensus on recommended setback distances. The 18 panelists were health care providers, public health practitioners, environmental advocates, and researchers/scientists. Consensus was defined as agreement of ≥70% of panelists. Content analysis of responses to Round 1 questions revealed four categories: recommend setback distances; do not recommend setback distances; recommend additional setback distances for vulnerable populations; do not recommend additional setback distances for vulnerable populations. In Round 2, panelists indicated their level of agreement with the statements in each category using a five-point Likert scale. Based on emerging consensus, statements within each category were collapsed into seven statements for Round 3: recommend set back distances of <¼ mile; ¼Ð ½ mile; 1±1 ¼ mile; and ≥ 2 mile; not feasible to recommend setback distances; recommend additional setbacks for vulnerable groups; not feasible to recommend additional setbacks for vulnerable groups. The panel reached consensus that setbacks of < ¼ mile should not be recommended and additional setbacks for vulnerable populations should be recommended. The panel did not reach consensus on recommendations for setbacks between ¼ and 2 miles. The results suggest that if setbacks are used the distances should be greater than ¼ of a mile from human activity, and that additional setbacks should be used for settings where vulnerable groups are found, including schools, daycare centers, and hospitals. The lack of consensus on setback distances between 1/4 and 2 miles reflects the limited health and exposure studies and need to better define exposures and track health.

Introduction

In the oil and gas extraction industry hydraulic fracturing, the injection of a mixture of water, chemicals, and sand under high pressure, has increased rapidly since the late 1990s. Critics

in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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have voiced concerns about long-term potential impacts on air, water, and soil quality that may accompany hydraulic fracturing and all stages of the processes associated with the development and transport of produced oil and gas (i.e. unconventional oil and gas development or UOGD) [1±9]. Additional concerns include the significant impact on surrounding communities caused by increased traffic, light, noise, and social disruption from this type of industrial development [10±13]. The entire process of UOGD, including oil and gas discovery, drilling, production, processing, waste management, and transport, includes many sources of air and water pollution, presenting risk factors for the environment, human health and community social structure.

Health and proximity to UOGD activity

Several recent studies have documented health outcomes related to closer proximity to UOGD activity. Steinzor, et al. [14], in their descriptive community study, documented increasing numbers of symptoms reported by residents as proximity to any type of UOGD facility decreased. Rabinowitz et al. [15] conducted a cross-sectional study to investigate the relationship between proximity to unconventional gas wells and reported health symptoms in a random sample of 429 residents of 180 households that had ground-fed water wells. GPS readings were taken at each household as residents completed a health survey. ArcGIS was used to calculate the distance of the home from natural gas wells. In this study, the number of symptoms reported per individual increased with household proximity to wells. Within 1 kilometer (km) of wells, residents reported more skin and respiratory symptoms compared to residents who lived at a greater distance.

Mckenzie et al. [16] estimated health risks for two populations in the Garfield County, Colorado gas fields: residents living less than or equal to 1/2 mile away from gas wells and those greater than ½ mile. They found that the populations living closer to gas wells were at higher risk of respiratory, neurological, and other health impacts and had a higher lifetime risk for cancer than those who lived at farther distances. For this study ambient air samples were collected from a fixed monitoring station located near unconventional natural gas development and residences, and from locations at the perimeters of four well pads. Methodology used by the Environmental Protection Agency were used to estimate non-cancer Hazard Indexes and excess lifetime cancer risks for exposures to hydrocarbons.

In a retrospective cohort study of 124,842 births in Colorado between 1996 and 2009, Mckenzie and colleagues [17] found an association between congenital heart defects and proximity and density of unconventional natural gas wells within 10 miles of maternal residence, using inverse distance weighted natural gas well counts as a measure of proximity and density. Results also suggested a possible association between neural tube defects and proximity and density. In another retrospective cohort study, Casey et al. [18] examined the relationship between exposure to unconventional gas development and birth outcomes in 10,946 births in Pennsylvania between 2009 and 2013. Unconventional gas development was modeled using distance from residence; dates of well pad preparation, drilling and hydraulic fracturing; and amount of production during pregnancy. Results showed an association between increased exposure and preterm birth, but no association between low APGAR scores, small for gestational age, or low term birthweight. Stacy and colleagues [19] also used an inverse distance weighted gas well count to examine the relationship of exposure to birth outcomes in their retrospective cohort study of 15,451 births in southwestern Pennsylvania between 2007 and 2010. Results showed increased exposure was associated with low birth weight and small for gestational age; it was not associated with preterm birth.

Tustin et al. [20] used self-reported symptoms to investigate associations between chronic rhinosinusitis, migraine, and fatigue, three conditions frequently reported in communities exposed to UOGD. Responses to self-report questionnaires were reviewed using standard criteria. Exposure was estimated using an ªactivity indexº [18] derived from four exposure metrics to account for different phases of well construction and production: distance from the residence; timing of well pad development, drilling, and hydraulic fracturing; and volume of gas produced. Results of the case-control analysis indicated that the highest quartile of the activity index was associated with increased odds of all three outcomes, when compared with the lowest quartile.

McKenzie et al. [21] investigated the relationship between acute lymphocytic leukemia and non-Hodgkin's lymphoma in children ages 0±24 and residential proximity to unconventional oil and gas development in Colorado. Cases and controls (i.e., children diagnosed with non-hematologic cancers) were diagnosed between 2000 and 2013 during rapid expansion of UNGD. Exposure was calculated using an inverse distance weighted (IDW) approach, first described by McKenzie et al. [17], to count all active oil and gas wells within 16.1 miles of each residence, giving greater weight to those that are closer. In the adjusted model, acute lymphocytic leukemia cases age 5±24 were 4.3 times likely to live in the highest well-count tercile as controls, with a monotonic increase across IDW tertiles (p for trend = 0.035). No such relationship was seen in leukemia cases 0±4 years or in non-Hodgkin's lymphoma cases of any age.

Rasmusen and colleagues [22] conducted a nested case-control study to investigate the relationship between asthma exacerbations and exposure to unconventional natural gas development. Using the Geisinger Clinic electronic health records, they identified cases of mild (i.e., new medication prescribed), moderate (i.e., emergency department visit), and severe (i.e., hospitalization) asthma exacerbations (n = 20,749; 1,870; and 4,782 respectively) treated at Geisinger between 2005 and 2012. Exposure was measured using the activity metric previously described by Casey [18]. In the adjusted model, mild, moderate, and severe asthma exacerbations were associated with high scores in each activity metric when compared to referents.

Setback distances and UOGD

A 2013 review of state setback distances for shale gas development shows the broad range of regulations in place at the time [23]. Of the 31 states in the review, 20 had setback restrictions specifically from buildings, 11 had none related to buildings. The restricted distances ranged from 100 feet (NY) to 1,000 feet (MD). California required setbacks, not from buildings but between wells and public roads. For this type of land-based restriction, the American Petroleum Institute recommended that ª. . .the wellsite and access road should be located as far as practical from occupied structures and places of assemblyº [24], offering a simple discretionary guideline. Setback restrictions for water sources were found in 12 states; 18 had none and one state had a discretionary standard. The regulated distance from water sources varied from 50 feet (OH) up to 2,000 feet (NY). A review of setback distances in urban areas of the Texas Barnett Shale showed a similarly broad range of regulations [25]. While the State permitted drilling within 200 feet of a dwelling, most municipalities employed longer distances; in Denton County these ranged from 300 to 1500 feet. Fry also found that 12 out of the 26 city setback ordinances reviewed had increased the distance over time±and none had been decreased. The author found that setback restrictions appeared to be politically rather than technically-based decisions and recommended greater reliance on ªadvanced emissions monitoringº to minimize discrepancies in determining appropriate setback distances.

Several authors have examined potential exposures related to existing setback distances. McCawley [26] conducted a study of air, noise and light impacts using the West Virginia state setback distance of 625 feet from the center of well pads. Measurable levels of dust and volatile organic chemicals, including one or more of benzene, toluene, ethylbenzene, and xylene, were found at all seven drilling sites where measurements were taken. Some benzene concentrations were above the ªminimum risk levelº for no health effects. Dispersal patterns were influenced by factors including multiple sources of emissions located throughout the well pad, local weather, topography, and wide fluctuation in levels of contaminants. Light levels, measured as skyglow, were zero during night time; ionizing radiation levels measured from filtered air-borne particulate were near zero as well. While average noise levels calculated for the duration of work at each site were not above the 70 dBA level recommended by the EPA, the noise at some locations was above that allowed by EPA regulation for vehicles engaged in interstate commerce and local noise ordinances. McCawley concluded that a setback distance of 625 feet cannot assure that nearby residents would not be exposed to drill site contaminants.

Haley et al. [27] reviewed current regulations and other aspects of setback distances used within the Marcellus, Barnett, and Niobrara shale plays. The most common setback distances from buildings were 300 and 500 feet, with a range of 150 to 1500 feet. The authors concluded that current setback distances are inadequate to protect residents in the case of explosions, radiant heat, toxic gas clouds, and air pollution from hydraulic fracturing activities; and that setback distances cannot provide absolute measures of safety, especially for vulnerable populations.

There is an increasing number of peer-reviewed articles addressing air quality impacts from UOGD (see for instance Physicians, Scientists and Engineers for Healthy Energy database) [28]. While these studies provide valuable science-based data that can support the rationale for regulating or not regulating setback distances, there remains a concern about the adequacy of health-based standards used to determine impacts from pollutant exposures.

In a critique of current methods of collecting air emissions data, Brown et al. [29] found that data collection and analysis of air pollution impacts from unconventional natural gas development cannot accurately assess human health impacts near UOGD sites. Specific findings were that ª1) current protocols used for assessing compliance with ambient air standards do not adequately determine the intensity, frequency or durations of the actual human exposures to the mixtures of toxic materials released at UOGD sites; 2) the typically used periodic 24 hour average measures can underestimate actual exposures by an order of magnitude; 3) reference standards are set in a form that inaccurately determines health risk because they do not fully consider the potential synergistic combinations of toxic air emissions; 4) air dispersion modeling shows that local weather conditions are strong determinates of individual exposures.º The authors recommend protocols that provide continuous chemical monitoring to show variations in exposure; modeling of local weather conditions to identify periods of high exposures; and sampling for chemical mixtures to identify the major components.

Two examples of air modeling studies provide context for assessing the need for setback distances. Olaguer [30] used a neighborhood scale dispersion model to simulate ozone formation resulting from emissions from UOGD in the Barnett Shale, focusing on both routine and nonroutine emission events (flares). The model predicted that both types of UOGD operations can have a significant impact on local ambient ozone levels. Modeled ozone levels increased at an approximate distance of 2km or more, at enhancement levels greater than 3 parts per billion (ppb). Modeled flare events could cause greater increases at distances >8km downwind. Ozone causes respiratory health effects including asthma and chronic obstructive pulmonary disease (COPD).

In another study, Brown et al. [31] describe a hypothetical case that demonstrates the direct effect of weather on exposure patterns of particulate matter (specifically $PM_{2.5}$) and volatile organic chemicals (VOCs) from unconventional natural gas infrastructure. The authors modeled the frequency and intensity of exposures to $PM_{2.5}$ and VOCs at a residence surrounded by three UOGD facilities. The hypothetical well pad, compressor and processing plant are 1 km, 2 km and 5 km distant from the residence. Modeled peak $PM_{2.5}$ and VOC exposures (defined as 2 standard deviations above the mean) during 14 months of well development occurred 83 times. Modeled compressor station emissions created 118 peak exposure levels and a gas processing plant produced 99 peak exposures over one year. The authors emphasize that local weather patterns combined with episodic emissions drive local exposure profiles.

While there is emerging evidence that proximity to UOGD activities is associated with chemical exposures and health outcomes, there is intense debate about "How close is too close?" The Delphi is an accepted method for reaching convergence of expert opinion about a specific topic, particularly when available data are inconclusive [32]. We conducted this Delphi study to arrive at expert consensus on two closely related questions: 1) the relationship between health outcomes and UOGD activities; and 2) appropriate setback distances for UOGD from human activity including residences, schools, work places, and farms. This paper reports the expert consensus on the question of appropriate setback distances; expert consensus on the question of relationship between health outcomes and UOGD activities will be presented in a subsequent report. Portions of this report on setback distances have been issued as a technical report by Southwest Pennsylvania Environmental Health Project www.environmentalhealthproject.org

Methods

Study design

This study used a conventional Delphi procedure [32–35], which can be viewed as a series of rounds. In each round, the participants (called "panelists") respond anonymously to a set of questions and then receive information about the responses of all other participants, including their own. Panelists are encouraged to re-assess their own responses on subsequent rounds with a goal of reaching consensus. The first round consists of a set of open-ended questions. Subsequent rounds consist of a set of statements to which panelists indicate their level of agreement on a five-point Likert scale. Three rounds are usually sufficient to reach consensus [35]. For this study consensus was defined as agreement of 70% of panelists, a decision point that is frequently used in Delphi studies [36–38].

Expert panel

There are few generally accepted criteria for inclusion on a Delphi panel [34] or agreement about the number of panelists required for a Delphi [39]. Early researchers who used this technique suggested the following criteria for inclusion: background and experience with the topic, capability to contribute, and willingness to revise their judgment to reach consensus [40]. More recent researchers suggest identifying stakeholders with interest in the topic: positional leaders, authors of publications in the scientific literature, and those with first-hand experience [41,42]. As Keeney et al. point out in their critical review of the technique, the definition of "expert" ranges from informed individuals to experts in the field [43]. The number of panelists required varies with the focus of the Delphi and the characteristics of the panelists. Generally, the more similar the members and the more narrow the focus of the investigation, the smaller the number, with 10–15 generally considered acceptable if the group is homogeneous; 15–30 if it is heterogeneous [43].

For this Delphi panel, selection criteria included: researchers whose work has been published in peer-reviewed journals and/or presented at national scientific meetings; scientists employed in regulatory agencies; and leaders in public policy and environmental advocacy who have been published in the grey literature. Potential panelists included representatives of federal and state agencies, environmental advocacy groups, health care providers, public health practitioners, and a range of researchers in areas including environmental science, toxicology, and social science. Invitations were sent via e-mail or the US Postal Service if no e-mail address was publicly available. The invitation included a consent to participate and the first round questions, along with an estimate of time commitment for participation. The study was reviewed and approved by the Duquesne University Institutional Review Board.

A total of 57 experts were invited to participate in this Delphi; 18 agreed to be panelists and returned the completed Round 1 questionnaire and consent form. Of those who did not participate, 23 simply did not respond to the invitation. A total of 18 provided a reason for declining, citing lack of time (n = 7), lack of expertise (n = 8), and no longer working in UOGD (n = 2).

Round 1

In the first round, panelists were asked to respond to the open-ended questions shown in Table 1, following these instructions:

> [a]We are interested in both gas and oil and know that the multiple steps in the production of these products differ. We understand that a panelist may have more expertise in one area than the other, so have constructed questions to allow for those differences. Where possible in your responses, please address all steps in the process from drilling site construction through delivery of the product to the consumer (e.g., well pad construction, well drilling, hydraulic fracturing, compressor stations, pumping stations, processing plants, impoundments, pipelines, and other steps in the process). In the questions below, the steps in this process are referred to as `relatedactivities'.[o]

Panelists were asked to return their responses within two weeks. Non-responders were sent a reminder at the end of two weeks. For those who requested additional time due to workload, travel, etc. the deadline was extended two weeks. The same procedure was followed in subsequent rounds.

Round 1 data analysis and development of Round 2 structured questionnaire

Content analysis was conducted on the qualitative responses to the open-ended questions in Round 1, with all responses independently coded by two members of the research team (CL

Table 1. Open-ended questions used in Round 1.

1	*What do you believe are appropriate set-back distances for hydraulic fracturing and related activities from places where people live, including single homes, multiple family dwellings, etc.? Please specify if your response is related to oil or gas extraction.*
2	*What do you believe are appropriate set-back distances for hydraulic fracturing and related activities from indoor places where people work including offices, hospitals, and schools? Please specify if your response is related to oil or gas extraction.*
3	*What do you believe are appropriate set-back distances for hydraulic fracturing and related activities from outdoor places where people work such as farms? Please specify if your response is related to oil or gas extraction.*
4	*What do you believe are appropriate set-back distances for hydraulic fracturing and related activities from places where people recreate or play such as parks? Please specify if your response is related to oil or gas extraction.*
5	*Should set-back distances differ for settings that include groups of vulnerable individuals, such as schools, day care centers, long- term care facilities, and if so, how? Please specify if your response is related to oil or gas extraction.*

Five open-ended questions were sent to all prospective panelists for their responses to initiate Round 1 of the Delphi study.

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and LG). Coding was compared for congruence. Similar responses were grouped into categories, for example, ªRecommended setback distancesº and ªCannot recommend setback distancesº as shown in the Results section. Within the category ªRecommended setback distancesº responses were grouped into mutually exclusive sub-categories. Responses to the question concerning vulnerable populations were grouped into two categories; both are shown in the Results section. All responses in each category were included on the structured questionnaire used for Round 2 and 3.

The structured questionnaire for Round 2 included all responses so that each panelist was able to see the complete range of responses in each category, with his/her own responses highlighted. Panelists were asked to indicate their level of agreement with each statement using a 5-point scale: strongly agree, agree, not sure, disagree, and strongly disagree and to provide a rationale for their decisions for those statements for which they strongly agreed or agreed.

Round 2 data analysis and development of Round 3 structured questionnaire

Responses to Round 2 were used to revise the structured questionnaire for Round 3. Statements within categories were collapsed to reflect emerging consensus within the panel. The Round 3 questionnaire provided the aggregated panelists' responses for each statement and the rationales provided by the individual panelists for their responses. For this final round, panelists were asked to review the distribution of responses and rationales provided and then indicate their level of agreement with each statement.

Results

Characteristics of panelists

The 18 panelists who agreed to participate and completed Round 1 self-identified as researchers/scientists, health care providers, environmental advocates, and public health practitioners. Self-reported areas of expertise included: medicine/health care, air quality, water quality, toxicology, environmental science, environmental health, public health, epidemiology, social science, policy, and risk analysis. The majority (83%) of the panelists hold earned doctoral degrees and reported working in their respective fields for a mean of 17.6 years (SD = 10), with a range of 4±35 years. In the area of UOGD specifically, they reported a mean 4.3 years (SD = 1.2), with a range of 2±6 years. The panelists represented a range of geographic regions throughout the United States; 50% were women. None of the authors participated as panelists. Of the 18 panelists, 14 (78%) participated in Round 2 and18 (100%) participated in Round 3.

Round 1

Responses to Questions #1- #4 were similar, with 9 panelists providing word-for-word the same response to all four open-ended questions. An additional four panelists provided the same response to three of the four questions. Only two panelists provided a different response to each of the four questions of setback distances from home, places of work, and places of recreation. Thus, all responses to these questions were considered together in the content analysis; two categories of responses, shown in Table 2, emerged.

There were 17 statements that included recommendations for specific setback distances from homes; places of work such as schools, office buildings, and farms; and recreational areas. Table 2 shows recommended distances ranged from 1/10 of a mile (0.1 km) to 2 miles (3.2 km). There were 18 statements that did not include recommendations for specific setback

Table 2. A comparison of exemplar statements recommending setback distances and exemplar statements not recommending setback distances from homes, places of work, or recreation areas.

Recommended setback distances
I defer to existing regulation: Center of well pads may not be located within 1/10 mile (0.1 km) of an occupied dwelling structure.
2/10 mile (0.3 km) for gas operations based on industry studies of blowouts, explosions and fires from drill rigs, compressor stations and pipelines.
Set-backs of at least 1/3 mile (0.5km) would be needed to prevent flow through documented pathways of subsurface contamination.
½ mile (0.8 km) for oil or natural gas extraction from office buildings and other indoor areas.
Minimum of 1 mile (1.6 km) for gas extraction
1 ¼ mile (2 km) from natural gas wells
At least 2 miles (3.2 km), maybe more
Cannot recommend setback distances
Due to our inability, with current information, to predict dispersal pathways accurately, I do not think safe set-back distances can be determined.
This is something that is difficult to determine because it depends on the hydrology and air currents.
My response applies to both oil and gas. . . .do not take a position on specific distances, in large part because there is no scientifically definitive distance beyond which health impacts would never occur. However, we believe that current setbacks from residential areas are much too short in all states.
I do not have an opinion on an appropriate set-back distance because I don't believe there is enough evidence to inform an opinion.
Again the distinction between oil and gas is not important. I think there are appropriate, science based setbacks that could be developed. I agree with the position that the ones that exist are not science based at all. . .and are based on political compromises.
There are no appropriate set-back distances for recreation areas near oil production. Ambient air quality is affected by VOCs. We have no proof of what constitutes a safe set-back distance. Cumulative effects have yet to be studied.

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distances. The exemplar statements in the Table 2 section ªCannot recommend setback distancesº reflect panelist's perspectives that there is insufficient information available to make recommendations. As one panelist pointed out, his lack of a specific recommendation did not imply that setback distances were not needed, just that he did not think it was possible to make a recommendation. All statements in each category were included on the structured questionnaire used for Round 2.

The content analysis revealed that responses to the question concerning setback distances for vulnerable populations differed from those to the first four questions. As shown in Table 3, panelist's responses fit into one of two categories: responses that argued for additional setback distances and responses that focused on the difficulties of establishing setback distances for vulnerable populations.

Eleven statements recommended additional setback distances for vulnerable populations. Vulnerable populations were defined by panelists to include: children, neonates, fetuses, embryos, pregnant women, elderly individuals, those with pre-existing medical or psychological conditions, and those with pre-existing respiratory conditions. Panelists included the following settings as places where vulnerable populations might be concentrated: schools, day care centers, hospitals, and long-term care facilities. Five statements focused on the difficulties of setting additional setback distances. As shown on Table 3, the panelists focused on the distribution of vulnerable individuals throughout the population, making the determination of setback distances to protect all vulnerable members of society difficult if not impossible.

The four categories of responses described above, and all statements within each, were used to create a structured questionnaire for Round 2. Panelists were asked to indicate their level of agreement on a 5-point Likert-type scale to a total of 51 statements and to provide a rationale

Table 3. A comparison of exemplar statements recommending additional setback distances for vulnerable populations and exemplar statements not recommending additional setback distances for vulnerable populations.

Panelists recommend additional considerations for vulnerable populations
Populations that are particularly sensitive to the toxins known and suspected to be associated with fracking activities should have special protections; this includes children, neonates, fetuses, embryos, pregnant women, elderly individuals, and those with pre-existing medical or psychological conditions.
I would consider this a case where additional restrictions would be important. Oil and/or gas operations near hospitals and schools should simply not be allowed. . .
Yes, greater setback distances are warranted for schools, daycare centers, long-term care facilities, etc. for both oil and gas extraction.
Larger setback distances in gas extraction are critical to larger vulnerable groups because one must take into consideration evacuation time and route in case of a catastrophic well or related infrastructure event.
Setbacks (gas) should definitely be farther from schools, day care centers where children are located and long-term facilities where people who already have compromised health don't need it further compromised by poor air quality from unconventional gas development.
Panelists do not recommend additional considerations for vulnerable populations
I am really unsure as to how to answer this because if air plumes travel and contribute to quality degradation of an entire region, it is likely that it would impact vulnerable populations regardless of physical proximity.
Regarding different set-backs for settings with vulnerable populations: Probably not. It appears that the most vulnerable populations are pregnant women and those with asthma, neither of which would necessarily be concentrated in specific facilities.
Vulnerable populations are distributed throughout the environment. This is therefore an inadequate calculation to consider.
The distances mentioned above are set to protect vulnerable persons as they are all a significant part of every society.
It makes sense to start with. . .longer setbacks on places used or inhabited by people with known vulnerabilities. However, there may be vulnerable individuals living, working, and spending time outdoors even in locations that are not specifically geared toward that population (for example, individuals with compromised immune systems, a history of cancer, or asthma).

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when they agreed with a statement. Their own statements from the first round were highlighted.

Round 2

Based on panelist's responses to the structured questionnaire, statements within categories were collapsed to reflect emerging consensus.

Recommended setback distances: In this category, the 17 statements were collapsed into four: less than ¼ mile; ¼Ð ½ mile; 1±1¼ miles; and 2 or more miles. (See Table 2 for exemplar statements.) All statements fit into one of these four groups, and emerging consensus in panelists' responses determined the cut-points used. These four statements were included on the structured questionnaire for Round 3.

Cannot recommend setback distances: Fourteen of the 18 statements were collapsed into one category which was restated as ªIt may not be feasible to recommend set back distances for the general populationº to more accurately reflect the content of the 14 statements. (See Table 2 for exemplar statements.) For these 14 statements, the proportion of panelists who agreed ranged from 54% to 92%. Four statements were excluded because they did not reflect emerging consensus.

Panelists recommend additional considerations for vulnerable populations: Ten of the 11 statements were collapsed into one category which was restated as ªRecommend additional consideration for vulnerable groupsº to more accurately reflect the content of the 10 statements. (See Table 3 for exemplar statements.) The proportion of panelists who agreed with the 10 statements ranged from 58% to 83%, indicating emerging consensus. One statement was excluded because it did not reflect emerging consensus.

Panelists do not recommend additional considerations for vulnerable populations: Three of the five statements were collapsed into one category which was restated as ªIt may not be feasible to recommend additional considerations (i.e., members of vulnerable populations are distributed throughout the population)º to more accurately reflect the content of the three statements. (See Table 3 for exemplar statements.) The proportion of panelists who agreed with the three statements ranged from 25% - 41%. Two statements were excluded because they did not differ from the panelist's responses to questions #1-#4.

The structured questionnaire for Round 3 included seven statements which are shown on Table 3. The questionnaire also included the distribution of panelist's responses and their rationales offered in Round 2. Panelists were asked to review the statements and rationales and then indicate their level of agreement/disagreement with each statement on the Round 3 questionnaire.

Round 3

The distribution of panelists' responses to the structured questionnaire in Round 3, along with the mean and standard deviation for each statement is shown in Table 4.

To determine consensus, we combined responses of ªagreeº and ªstrongly agreeº to determine the % of panelist agreement with a statement and responses of ªdisagreeº and ªstrongly disagreeº to determine the % panelist disagreement with a statement. Within the category ªrecommended setback distancesº, panelists reached consensus on the statement ªless than ¼ mileº. A total of 89% of panelists disagreed with that statement (i.e., 11% disagreed plus 78% strongly disagreed for a total of 89%), reaching the 70% set for consensus in this Delphi.

Panelists did not reach consensus on the statement ª ¼Ð ½ mileº. For this statement, 66% of panelists disagreed with the statement, 22% were unsure, and only 11% of panelists agreed. Panelists did not reach consensus on the statement ª1±1¼ milesº, 50% agreed, 28% were unsure, and 22% disagreed. Panelists did not reach consensus on the statement ªat least 2 milesº; 34% agreed, 44% were unsure, and 22% disagreed. For the statement ªIt may not be feasible to recommend setback distances for the general populationº, 67% of panelists agreed, 6% were unsure, 28% disagreed.

Regarding setback distances for vulnerable populations, panelists reached consensus on the statement ªRecommend additional consideration for vulnerable groupsº with 87% agreeing. Panelists did not reach consensus on the statement ªIt may not be feasible to recommend additional considerations for vulnerable groupsº, with panelists nearly equally divided between agreement and disagreement with the statement. See S1 Chart for a visual representation of Delphi results.

Table 4. Distribution of panelists' levels of agreement with statements used in Round 3 and median scores.

	1	2	3	4	5	Mean (SD)
Recommend less than ¼ mile setback	0%	0%	11%	11%	78%	4.67 (0.65)
Recommend ¼Ð ½ mile setback	0%	11%	22%	22%	44%	4.0 (1.03)
Recommend 1±1¼ miles setback	6%	44%	28%	11%	11%	2.78 (1.05)
Recommend at least 2 miles setback	17%	17%	44%	11%	11%	2.83 (1.14)
It may not be feasible to recommend setback distances for the general population	28%	39%	6%	22%	6%	2.17 (1.09)
Recommend additional consideration for vulnerable groups	67%	22%	11%	0%	0%	1.44 (0.67)
It may not be feasible to recommend additional considerations for vulnerable groups	6%	33%	6%	33%	22%	3.17 (1.26)

1 = strongly agree; 2 = agree; 3 = not sure; 4 = disagree; 5 = strongly disagree.

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Discussion

There is significant public and scholarly debate about the relationship between proximity to these industrial activities and human health. The Delphi provides a unique tool to learn how experts on a particular topic apply their knowledge and experience to a complex problem, and to determine whether a convergence of opinion can be established [32±35, 41±43]. In this study we used the Delphi method to address the issue of appropriate setback distances for UOGD from places where humans live, work, and play. The intent of this Delphi was to reach expert consensus on appropriate setback distances from homes, workplaces, and recreation areas in general, and for vulnerable populations in particular.

The responses to the open-ended questions in Round 1 generated a set of statements that expanded the question of setback distances. The panelist's responses reflected their opinions about the adequacy of both the evidence available to answer the question and the ability of setback distances to protect the health of the public, rather than providing simple statements of specific distances. Accordingly, their responses were grouped into four categories: recommendations for specific setback distances from places of human activity; no recommendations for specific setback distances from places of human activity; recommendations for additional setback distances for vulnerable populations; no recommendations for additional setback distances for vulnerable populations.

Round 2 responses were collapsed into seven statements, based on panelists' responses to the individual statements and emerging consensus. Four statements focused on specific setback distances from places where people live, work, or play: *Recommend <¼ mile; Recommend ¼—½ mile; Recommend 1–1¼ mile; Recommend 2 miles or more*. Three additional statements focused on feasibility and vulnerable populations: *It may not be feasible to recommend setback distances; Recommend additional considerations for vulnerable populations; It may not be feasible to recommend additional considerations for vulnerable groups*.

Setbacks of <¼ mile are not sufficient

Panelists reached consensus that setback distances of <¼ mile were not sufficient but were not able to reach consensus for the longer setback distances suggested by panelists (i.e., ¼Ð ½ mile, 1±1¼ mile, and 2 miles or more). A total of 67% of panelist agreed with the statement that it may not be feasible to establish setback distances, very nearly reaching consensus. Taken together, these results suggest that while these panelists agreed that ¼ of a mile is ªtoo closeº they did not feel able to recommend a specific distance that would protect the health of the public. Failure to reach consensus about setback distances between ¼ and 2 miles reflects published studies that have identified a variety of health effects and evidence of exposure at various points within that range [14, 15, 17±22]. Nevertheless, panelists were clear that current setback regulations of less than ¼ mile are not adequate.

Recommend additional setbacks for vulnerable populations or settings

Panelists reached consensus that additional setback distances should be established for vulnerable populations or settings. Vulnerable groups were defined by the panelists as children, neonates, fetuses, embryos, pregnant women, elderly individuals, those with pre-existing medical or psychological conditions, and those with pre-existing respiratory conditions. Vulnerable settings were defined as schools, day care centers, hospitals, and long-term care facilities. At the same time, panelists were split as to whether such consideration was actually feasible, recognizing that since vulnerable people are distributed throughout the general population it would be difficult if not impossible to give them extra consideration. Yet some suggested that where vulnerable individuals gather, such as in schools and playing fields, setbacks may be useful.

Limitations and further research

The results of this Delphi should be interpreted with caution, as they reflect the expert opinion of one panel. It is possible that another panel would reach a different consensus, and further research is warranted. In addition, using 70% as the decision-point for consensus means that some portion of the panel is not in agreement. Therefore, we included in the results section the percentage of agreement and the mean and standard deviation of the Likert score for each statement in an effort to be as transparent as possible. While the panel had a broad range of relevant expertise in public and environmental health and many years of experience in a variety of professional activities, the panel would have been strengthened by representation from the petroleum industry. Future research should purposefully include such scientists, researchers, and practitioners. Not all panelists participated in all rounds, however, all panelists who participated in Round 1 participated in Round 3.

Conclusion

In conclusion, the results of this Delphi study suggest that if setbacks are used the distances should be greater than ¼ of a mile from any area where human activity takes place, and that additional setbacks should be used for settings where vulnerable groups are found, including schools, daycare centers, and hospitals. The panel did not reach a consensus on setback distances between ¼ and 2 miles. While both health effects and exposures have been reported in the literature and are consistent with scientific reports, there is uncertainty with respect to levels and types of exposures and the health responses further from the wells. One report has suggested that site-specific air measures are needed. Levels of exposure have been documented based on analysis and air modeling in both air and water within ¼ of a mile. Although air modeling indicates air exposures in the ¼ to 2-mile range, it is difficult to measure due to localized weather variability. Health effects are reported in the peer-reviewed literature for respiratory disease and dermatologic effects, however the health effects could be related to the presence of other sources of pollution. Thus, failure to achieve consensus on the range of setback distances appears to reflect uncertainties based on limited data on real-time emissions from UOGD, the limited scientific studies available and the presence of periods of potential high exposures.

Supporting information

S1 Chart. Flow chart of results of Rounds 1±3 for statements that recommend setbacks for UOGD infrastructure. Consensus = 70%.
(PDF)

S1 Dataset. Round 1 responses.
(PDF)

S2 Dataset. Round 2 responses.
(XLSX)

S3 Dataset. Round 3 responses.
(XLSX)

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ATTACHMENT C

STUDY 8

Human health risk assessment of air emissions from development of unconventional natural gas resources

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Human health risk assessment of air emissions from development of unconventional natural gas resources☆,☆☆

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ABSTRACT

Background: Technological advances (e.g. directional drilling, hydraulic fracturing), have led to increases in unconventional natural gas development (NGD), raising questions about health impacts.
Objectives: We estimated health risks for exposures to air emissions from a NGD project in Garfield County, Colorado with the objective of supporting risk prevention recommendations in a health impact assessment (HIA).
Methods: We used EPA guidance to estimate chronic and subchronic non-cancer hazard indices and cancer risks from exposure to hydrocarbons for two populations: (1) residents living >½ mile from wells and (2) residents living ≤½ mile from wells.
Results: Residents living ≤½ mile from wells are at greater risk for health effects from NGD than are residents living >½ mile from wells. Subchronic exposures to air pollutants during well completion activities present the greatest potential for health effects. The subchronic non-cancer hazard index (HI) of 5 for residents ≤½ mile from wells was driven primarily by exposure to trimethylbenzenes, xylenes, and aliphatic hydrocarbons. Chronic HIs were 1 and 0.4. for residents ≤½ mile from wells and >½ mile from wells, respectively. Cumulative cancer risks were 10 in a million and 6 in a million for residents living ≤½ mile and >½ mile from wells, respectively, with benzene as the major contributor to the risk.
Conclusions: Risk assessment can be used in HIAs to direct health risk prevention strategies. Risk management approaches should focus on reducing exposures to emissions during well completions. These preliminary results indicate that health effects resulting from air emissions during unconventional NGD warrant further study. Prospective studies should focus on health effects associated with air pollution.

1. Introduction

The United States (US) holds large reserves of unconventional natural gas resources in coalbeds, shale, and tight sands. Technological advances, such as directional drilling and hydraulic fracturing, have led to a rapid increase in the development of these resources. For example, shale gas production had an average annual growth rate of 48% over the 2006 to 2010 period and is projected to grow almost fourfold from 2009 to 2035 (US EIA, 2011). The number of unconventional natural gas wells in the US rose from 18,485 in 2004 to 25,145 in 2007 and is expected to continue increasing through at least 2020 (Vidas and Hugman, 2008). With this expansion, it is becoming increasingly common for unconventional natural gas development (NGD) to occur near where people live, work, and play. People living near these development sites are raising public health concerns, as rapid NGD exposes more people to various potential stressors (COGCC, 2009a).

The process of unconventional NGD is typically divided into two phases: well development and production (US EPA, 2010a; US DOE, 2009). Well development involves pad preparation, well drilling, and well completion. The well completion process has three primary stages: 1) completion transitions (concrete well plugs are installed in wells to separate fracturing stages and then drilled out to release gas for production); 2) hydraulic fracturing ("fracking": the high pressure injection of water, chemicals, and propants into the drilled well to release the natural gas); and 3) flowback, the return of fracking and geologic fluids, liquid hydrocarbons ("condensate") and natural gas to the surface (US EPA, 2010a; US DOE, 2009). Once development is

Abbreviations: BTEX, benzene, toluene, ethylbenzene, and xylenes; COGCC, Colorado Oil and Gas Conservation Commission; HAP, hazardous air pollutant; HI, hazard index; HIA, health impact assessment; HQ, hazard quotient; NATA, National Air Toxics Assessment; NGD, natural gas development.

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complete, the "salable" gas is collected, processed, and distributed. While methane is the primary constituent of natural gas, it contains many other chemicals, including alkanes, benzene, and other aromatic hydrocarbons (TERC, 2009).

As shown by ambient air studies in Colorado, Texas, and Wyoming, the NGD process results in direct and fugitive air emissions of a complex mixture of pollutants from the natural gas resource itself as well as diesel engines, tanks containing produced water, and on site materials used in production, such as drilling muds and fracking fluids (CDPHE, 2009; Frazier, 2009; Walther, 2011; Zielinska et al., 2011). The specific contribution of each of these potential NGD sources has yet to be ascertained and pollutants such as petroleum hydrocarbons are likely to be emitted from several of these NGD sources. This complex mixture of chemicals and resultant secondary air pollutants, such as ozone, can be transported to nearby residences and population centers (Walther, 2011; GCPH, 2010).

Multiple studies on inhalation exposure to petroleum hydrocarbons in occupational settings as well as residences near refineries, oil spills and petrol stations indicate an increased risk of eye irritation and headaches, asthma symptoms, acute childhood leukemia, acute myelogenous leukemia, and multiple myeloma (Glass et al., 2003; Kirkeleit et al., 2008; Brosselin et al., 2009; Kim et al., 2009; White et al., 2009). Many of the petroleum hydrocarbons observed in these studies are present in and around NGD sites (TERC, 2009). Some, such as benzene, ethylbenzene, toluene, and xylene (BTEX) have robust exposure and toxicity knowledge bases, while toxicity information for others, such as heptane, octane, and diethylbenzene, is more limited. Assessments in Colorado have concluded that ambient benzene levels demonstrate an increased potential risk of developing cancer as well as chronic and acute non-cancer health effects in areas of Garfield County Colorado where NGD is the only major industry other than agriculture (CDPHE, 2007; Coons and Walker, 2008; CDPHE, 2010). Health effects associated with benzene include acute and chronic nonlymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, anemia, and other blood disorders and immunological effects. (ATSDR, 2007a, IRIS, 2011). In addition, maternal exposure to ambient levels of benzene recently has been associated with an increase in birth prevalence of neural tube defects (Lupo et al., 2011). Health effects of xylene exposure include eye, nose, and throat irritation, difficulty in breathing, impaired lung function, and nervous system impairment (ATSDR, 2007b). In addition, inhalation of xylenes, benzene, and alkanes can adversely affect the nervous system (Carpenter et al., 1978; Nilsen et al., 1988; Galvin and Marashi, 1999; ATSDR, 2007a; ATSDR, 2007b).

Previous assessments are limited in that they were not able to distinguish between risks from ambient air pollution and specific NGD stages, such as well completions or risks between residents living near wells and residents living further from wells. We were able to isolate risks to residents living near wells during the flowback stage of well completions by using air quality data collected at the perimeter of the wells while flowback was occurring.

Battlement Mesa (population ~5000) located in rural Garfield County, Colorado is one community experiencing the rapid expansion of NGD in an unconventional tight sand resource. A NGD operator has proposed developing 200 gas wells on 9 well pads located as close as 500 ft from residences. Colorado Oil and Gas Commission (COGCC) rules allow natural gas wells to be placed as close as 150 ft from residences (COGCC, 2009b). Because of community concerns, as described elsewhere, we conducted a health impact assessment (HIA) to assess how the project may impact public health (Witter et al., 2011), working with a range of stakeholders to identify the potential public health risks and benefits.

In this article, we illustrate how a risk assessment was used to support elements of the HIA process and inform risk prevention recommendations by estimating chronic and subchronic non-cancer hazard indices (HIs) and lifetime excess cancer risks due to NGD air emissions.

2. Methods

We used standard United States Environmental Protection Agency (EPA) methodology to estimate non-cancer HIs and excess lifetime cancer risks for exposures to hydrocarbons (US EPA, 1989; US EPA, 2004) using residential exposure scenarios developed for the NGD project. We used air toxics data collected in Garfield County from January 2008 to November 2010 as part of a special study of short term exposures as well as on-going ambient air monitoring program data to estimate subchronic and chronic exposures and health risks (Frazier, 2009; GCPH, 2009; GCPH, 2010; GCPH, 2011; Antero, 2010).

2.1. Sample collection and analysis

All samples were collected and analyzed according to published EPA methods. Analyses were conducted by EPA certified laboratories. The Garfield County Department of Public Health (GCPH) and Olsson Associates, Inc. (Olsson) collected ambient air samples into evacuated SUMMA® passivated stainless-steel canisters over 24-hour intervals. The GCPH collected the samples from a fixed monitoring station and along the perimeters of four well pads and shipped samples to Eastern Research Group for analysis of 78 hydrocarbons using EPA's compendium method TO-12, Method for the Determination of Non-Methane Organic Compounds in Ambient Air Using Cyrogenic Preconcentration and Direct Flame Ionization Detection (US EPA, 1999). Olsson collected samples along the perimeter of one well pad and shipped samples to Atmospheric Analysis and Consulting, Inc. for analysis of 56 hydrocarbons (a subset of the 78 hydrocarbons determined by Eastern Research Group) using method TO-12. Per method TO-12, a fixed volume of sample was cryogenically concentrated and then desorbed onto a gas chromatography column equipped with a flame ionization detector. Chemicals were identified by retention time and reported in a concentration of parts per billion carbon (ppbC). The ppbC values were converted to micrograms per cubic meter ($\mu g/m^3$) at 01.325 kPa and 298.15 K.

Two different sets of samples were collected from rural (population < 50,000) areas in western Garfield County over varying time periods. The main economy, aside from the NGD industry, of western Garfield County is agricultural. There is no other major industry.

2.1.1. NGD area samples

The GCPH collected ambient air samples every six days between January 2008 and November 2010 (163 samples) from a fixed monitoring station located in the midst of rural home sites and ranches and NGD, during both well development and production. The site is located on top of a small hill and 4 miles upwind of other potential emission sources, such as a major highway (Interstate-70) and the town of Silt, CO (GCPH, 2009; GCPH, 2010; GCPH, 2011).

2.1.2. Well completion samples

The GCPH collected 16 ambient air samples at each cardinal direction along 4 well pad perimeters (130 to 500 ft from the well pad center) in rural Garfield County during well completion activities. The samples were collected on the perimeter of 4 well pads being developed by 4 different natural gas operators in summer 2008 (Frazier, 2009). The GCPH worked closely with the NGD operators to ensure these air samples were collected during the period while at least one well was on uncontrolled (emissions not controlled) flowback into collection tanks vented directly to the air. The number of wells on each pad and other activities occurring on the pad were not documented. Samples were collected over 24 to 27-hour intervals, and samples included emissions from both uncontrolled flowback and diesel engines (i.e., from. trucks and generators supporting completion activities). In addition, the GCPH collected a background sample 0.33 to 1 mile from each well pad (Frazier, 2009). The highest hydrocarbon levels corresponded to samples collected directly downwind of the tanks (Frazier, 2009; Antero, 2010). The lowest hydrocarbon levels corresponded either to background samples or samples collected upwind of the flowback tanks (Frazier, 2009; Antero, 2010).

Antero Resources Inc., a natural gas operator, contracted Olsson to collect eight 24-hour integrated ambient air samples at each cardinal direction at 350 and 500 ft from the well pad center during well completion activities conducted on one of their well pads in summer 2010 (Antero, 2010). Of the 12 wells on this pad, 8 were producing salable natural gas; 1 had been drilled but not completed; 2 were being hydraulically fractured during daytime hours, with ensuing uncontrolled flowback during nighttime hours; and 1 was on uncontrolled flowback during nighttime hours.

All five well pads are located in areas with active gas production, approximately 1 mile from Interstate-70.

2.2. Data assessment

We evaluated outliers and compared distributions of chemical concentrations from NGD area and well completion samples using Q–Q plots and the Mann–Whitney *U* test, respectively, in EPA's ProUCL version 4.00.05 software (US EPA, 2010b). The Mann–Whitney *U* test was used because the measurement data were not normally distributed. Distributions were considered as significantly different at an alpha of 0.05. Per EPA guidance, we assigned the exposure concentration as either the 95% upper confidence limit (UCL) of the mean concentration for compounds found in 10 or more samples or the maximum detected concentration for compounds found in more than 1 but fewer than 10 samples. This latter category included three compounds: 1,3-butadiene, 2,2,4-trimethylpentane, and styrene in the well completion samples. EPA's ProUCL software was used to select appropriate methods based on sample distributions and detection frequency for computing 95% UCLs of the mean concentration (US EPA, 2010b).

2.3. Exposure assessment

Risks were estimated for two populations: (1) residents >½ mile from wells; and (2) residents ≤½ mile from wells. We defined residents ≤½ mile from wells as living near wells, based on residents reporting odor complaints attributed to gas wells in the summer of 2010 (COGCC, 2011).

Exposure scenarios were developed for chronic non-cancer HIs and cancer risks. For both populations, we assumed a 30-year project duration based on an estimated 5-year well development period for all well pads, followed by 20 to 30 years of production. We assumed a resident lives, works, and otherwise remains within the town 24 h/day, 350 days/year and that lifetime of a resident is 70 years, based on standard EPA reasonable maximum exposure (RME) defaults (US EPA, 1989).

2.3.1. Residents >½ mile from well pads

As illustrated in Fig. 1, data from the NGD area samples were used to estimate chronic and subchronic risks for residents >½ mile from well development and production throughout the project. The exposure concentrations for this population were the 95% UCL on the mean concentration and median concentration from the 163 NGD samples.

2.3.2. Residents ≤½ mile from well pads

To evaluate subchronic non-cancer HIs from well completion emissions, we estimated that a resident lives ≤½ mile from two well pads resulting a 20-month exposure duration based on 2 weeks per well for completion and 20 wells per pad, assuming some overlap in between activities. The subchronic exposure concentrations for this population were the 95% UCL on the mean concentration and the median concentration from the 24 well completion samples. To evaluate chronic risks to residents ≤½ mile from wells throughout the NGD project, we calculated a time-weighted exposure concentration (C_{S+c}) to account for exposure to emissions from well completions for 20-months followed by 340 months of exposure to emissions from the NGD area using the following formula:

$$C_{S+c} = (C_c \times ED_c/ED) + (C_S \times ED_S/ED)$$

where:

C_c Chronic exposure point concentration (μg/m^3) based on the 95% UCL of the mean concentration or median concentration from the 163 NGD area samples

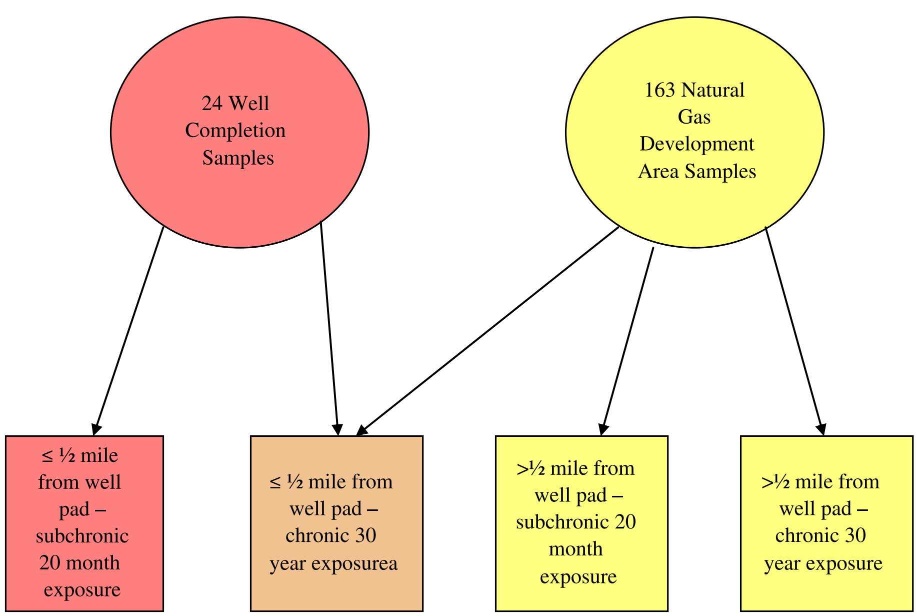

Fig. 1. Relationship between completion samples and natural gas development area samples and residents living ≤½ mile and >½ mile from wells. [a]Time weighted average based on 20-month contribution from well completion samples and 340-month contribution from natural gas development samples.

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ED_c Chronic exposure duration
C_S Subchronic exposure point concentration (μg/m^3) based on the 95% UCL of the mean concentration or median concentration from the 24 well completion samples
ED_S Subchronic exposure duration
ED Total exposure duration

2.4. Toxicity assessment and risk characterization

For non-carcinogens, we expressed inhalation toxicity measurements as a reference concentration (RfC in units of μg/m^3 air). We used chronic RfCs to evaluate long-term exposures of 30 years and subchronic RfCs to evaluate subchronic exposures of 20-months. If a subchronic RfC was not available, we used the chronic RfC. We obtained RfCs from (in order of preference) EPA's Integrated Risk Information System (IRIS) (US EPA, 2011), California Environmental Protection Agency (CalEPA) (CalEPA, 2003), EPA's Provisional Peer-Reviewed Toxicity Values (ORNL, 2009), and Health Effects Assessment Summary Tables (US EPA, 1997). We used surrogate RfCs according to EPA guidance for C_5 to C_{18} aliphatic and C_6 to C_{18} aromatic hydrocarbons which did not have a chemical-specific toxicity value (US EPA, 2009a). We derived semi-quantitative hazards, in terms of the hazard quotient (HQ), defined as the ratio between an estimated exposure concentration and RfC. We summed HQs for individual compounds to estimate the total cumulative HI. We then separated HQs specific to neurological, respiratory, hematological, and developmental effects and calculated a cumulative HI for each of these specific effects.

For carcinogens, we expressed inhalation toxicity measurements as inhalation unit risk (IUR) in units of risk per μg/m^3. We used IURs from EPA's IRIS (US EPA, 2011) when available or the CalEPA (CalEPA, 2003). The lifetime cancer risk for each compound was derived by multiplying estimated exposure concentration by the IUR. We summed cancer risks for individual compounds to estimate the cumulative cancer risk. Risks are expressed as excess cancers per 1 million population based on exposure over 30 years.

Toxicity values (i.e., RfCs or IURs) or a surrogate toxicity value were available for 45 out of 78 hydrocarbons measured. We performed a quantitative risk assessment for these hydrocarbons. The remaining 33 hydrocarbons were considered qualitatively in the risk assessment.

3. Results

3.1. Data assessment

Evaluation of potential outliers revealed no sampling, analytical, or other anomalies were associated with the outliers. In addition, removal of potential outliers from the NGD area samples did not change the final HIs and cancer risks. Potential outliers in the well completion samples were associated with samples collected downwind from flowback tanks and are representative of emissions during flowback. Therefore, no data was removed from either data set.

Descriptive statistics for concentrations of the hydrocarbons used in the quantitative risk assessment are presented in Table 1. A list of the hydrocarbons detected in the samples that were considered qualitatively in the risk assessment because toxicity values were not available is presented in Table 2. Descriptive statistics for all hydrocarbons are available in Supplemental Table 1. Two thirds more hydrocarbons were detected at a frequency of 100% in the well completion samples (38 hydrocarbons) than in the NGD area samples (23 hydrocarbons). Generally, the highest alkane and aromatic hydrocarbon median concentrations were observed in the well completion samples, while the highest median concentrations of several alkenes were observed in the NGD area samples. Median concentrations of benzene, ethylbenzene, toluene, and m-xylene/p-xlyene were 2.7, 4.5, 4.3, and 9 times higher in the well completion samples than in the NGD area samples, respectively. Wilcoxon–Mann–Whitney test results indicate that

Table 1
Descriptive statistics for hydrocarbon concentrations with toxicity values in 24-hour integrated samples collected in NGD area and samples collected during well completions.

Hydrocarbon (μg/m^3)	NGD area sample results[a]							Well completion sample results[b]						
	No.	% > MDL	Med	SD	95% UCL[c]	Min	Max	No.	% > MDL	Med	SD	95% UCL[c]	Min	Max
1,2,3-Trimethylbenzene	163	39	0.11	0.095	0.099	0.022	0.85	24	83	0.84	2.3	3.2	0.055	12
1,2,4-Trimethylbenzene	163	96	0.18	0.34	0.31	0.063	3.1	24	100	1.7	17	21	0.44	83
1,3,5-Trimethylbenzene	163	83	0.12	0.13	0.175	0.024	1.2	24	100	1.3	16	19.5	0.33	78
1,3-Butadiene	163	7	0.11	0.020	0.0465	0.025	0.15	16	56	0.11	0.021	NC	0.068	0.17
Benzene	163	100	0.95	1.3	1.7	0.096	14	24	100	2.6	14	20	0.94	69
Cyclohexane	163	100	2.1	8.3	6.2	0.11	105	24	100	5.3	43	58	2.21	200
Ethylbenzene	163	95	0.17	0.73	0.415	0.056	8.1	24	100	0.77	47	54	0.25	230
Isopropylbenzene	163	38	0.15	0.053	0.074	0.020	0.33	24	67	0.33	1.0	1.0	0.0	4.8
Methylcyclohexane	163	100	3.7	4.0	6.3	0.15	24	24	100	14	149	190	3.1	720
m-Xylene/p-Xylene	163	100	0.87	1.2	1.3	0.16	9.9	24	100	7.8	194	240	2.0	880
n-Hexane	163	100	4.0	4.2	6.7	0.13	25	24	100	7.7	57	80	1.7	255
n-Nonane	163	99	0.44	0.49	0.66	0.064	3.1	24	100	3.6	61	76	1.2	300
n-Pentane	163	100	9.1	9.8	14	0.23	62	24	100	11	156	210	3.9	550
n-Propylbenzene	163	66	0.10	0.068	0.10	0.032	0.71	24	88	0.64	2.4	3.3	0.098	12
o-Xylene	163	97	0.22	0.33	0.33	0.064	3.6	24	100	1.2	40	48.5	0.38	190
Propylene	163	100	0.34	0.23	0.40	0.11	2.5	24	100	0.41	0.34	0.60	0.16	1.9
Styrene	163	15	0.15	0.26	0.13	0.017	3.4	24	21	0.13	1.2	NC	0.23	5.9
Toluene	163	100	1.8	6.2	4.8	0.11	79	24	100	7.8	67	92	2.7	320
Aliphatic hydrocarbons C_5–C_8[d]	163	NC	29	NA	44	1.7	220	24	NC	56	NA	780	24	2700
Aliphatic hydrocarbons C_9–C_{18}[e]	163	NC	1.3	NA	14	0.18	400	24	NC	7.9	NA	100	1.4	390
Aromatic hydrocarbons C_9–C_{18}[f]	163	NC	0.57	NA	0.695	0.17	5.6	24	NC	3.7	NA	27	0.71	120

Abbreviations: Max, maximum detected concentration; Med, median; Min, minimum detected concentration; NGD, natural gas development; NC, not calculated; No., number of samples; SD, standard deviation; % > MDL, percent greater than method detection limit; μg/m^3 micrograms per cubic meter; 95% UCL 95% upper confidence limit on the mean.
[a] Samples collected at one site every 6 six days between 2008 and 2010.
[b] Samples collected at four separate sites in summer 2008 and one site in summer 2010.
[c] Calculated using EPA's ProUCL version 4.00.05 software (US EPA, 2010b).
[d] Sum of 2,2,2-trimethylpentane, 2,2,4-trimethylpentane, 2,2-dimethylbutane, 2,3,4-trimethylpentane, 2,3-dimethylbutane, 2,3-dimethylpentane, 2,4-dimethylpentane, 2-methylheptane, 2-methylhexane, 2-methylpentane, 3-methylheptane, 3-methylhexane, 3-methylpentane, cyclopentane, isopentane, methylcyclopentane, n-heptane, n-octane.
[e] Sum of n-decane, n-dodecane, n-tridecane, n-undecane.
[f] Sum of m-diethylbenzene, m-ethyltoluene, o-ethyltoluene, p-diethylbenzene, p-ethyltoluene.

Table 2
Detection frequencies of hydrocarbons without toxicity values detected in NGD area or well completion samples.

Hydrocarbon	NGD area sample[a] detection frequency (%)	Well completion sample[b] detection frequency (%)
1-Dodecene	36	81
1-Heptene	94	100
1-Hexene	63	79
1-Nonene	52	94
1-Octene	29	75
1-Pentene	98	79
1-Tridecene	7	38
1-Undecene	28	81
2-Ethyl-1-butene	1	0
2-Methyl-1-butene	29	44
2-Methyl-1-pentene	1	6
2-Methyl-2-butene	36	69
3-Methyl-1-butene	6	6
4-Methyl-1-pentene	16	69
Acetylene	100	92
a-Pinene	63	100
b-Pinene	10	44
cis-2-Butene	58	75
cis-2-Hexene	13	81
cis-2-Pentene	38	54
Cyclopentene	44	94
Ethane	100	100
Ethylene	100	100
Isobutane	100	100
Isobutene/1-Butene	73	44
Isoprene	71	96
n-Butane	98	100
Propane	100	100
Propyne	1	0
trans-2-Butene	80	75
trans-2-Hexene	1	6
trans-2-Pentene	55	83

Abbreviations: NGD, natural gas development.
[a] Samples collected at one site every 6 six days between 2008 and 2010.
[b] Samples collected at four separate sites in summer 2008 and one site in summer 2010.

concentrations of hydrocarbons from well completion samples were significantly higher than concentrations from NGD area samples ($p<0.05$) with the exception of 1,2,3-trimethylbenzene, n-pentane, 1,3-butadiene, isopropylbenzene, n-propylbenzene, propylene, and styrene (Supplemental Table 2).

3.2. Non-cancer hazard indices

Table 3 presents chronic and subchronic RfCs used in calculating non-cancer HIs, as well critical effects and other effects. Chronic non-cancer HQ and HI estimates based on ambient air concentrations are presented in Table 4. The total chronic HIs based on the 95% UCL of the mean concentration were 0.4 for residents >½ mile from wells and 1 for residents ≤½ mile from wells. Most of the chronic non-cancer hazard is attributed to neurological effects with neurological HIs of 0.3 for residents >½ mile from wells and 0.9 for residents ≤½ mile from wells.

Total subchronic non-cancer HQs and HI estimates are presented in Table 5. The total subchronic HIs based on the 95% UCL of the mean concentration were 0.2 for residents >½ mile from wells and 5 for residents ≤½ mile from wells. The subchronic non-cancer hazard for residents >½ mile from wells is attributed mostly to respiratory effects (HI = 0.2), while the subchronic hazard for residents ≤½ mile from wells is attributed to neurological (HI = 4), respiratory (HI = 2), hematologic (HI = 3), and developmental (HI = 1) effects.

For residents >½ mile from wells, aliphatic hydrocarbons (51%), trimethylbenzenes (22%), and benzene (14%) are primary contributors to the chronic non-cancer HI. For residents ≤½ mile from wells, trimethylbenzenes (45%), aliphatic hydrocarbons (32%), and xylenes (17%) are primary contributors to the chronic non-cancer HI, and trimethylbenzenes (46%), aliphatic hydrocarbons (21%) and xylenes (15%) also are primary contributors to the subchronic HI.

3.3. Cancer risks

Cancer risk estimates calculated based on measured ambient air concentrations are presented in Table 6. The cumulative cancer risks based on the 95% UCL of the mean concentration were 6 in a million for residents >½ from wells and 10 in a million for residents ≤½ mile from wells. Benzene (84%) and 1,3-butadiene (9%) were the primary contributors to cumulative cancer risk for residents >½ mile from wells. Benzene (67%) and ethylbenzene (27%) were the primary contributors to cumulative cancer risk for residents ≤½ mile from wells.

4. Discussion

Our results show that the non-cancer HI from air emissions due to natural gas development is greater for residents living closer to wells. Our greatest HI corresponds to the relatively short-term (i.e., subchronic), but high emission, well completion period. This HI is driven principally by exposure to trimethylbenzenes, aliphatic hydrocarbons, and xylenes, all of which have neurological and/or respiratory effects. We also calculated higher cancer risks for residents living nearer to wells as compared to residents residing further from wells. Benzene is the major contributor to lifetime excess cancer risk for both scenarios. It also is notable that these increased risk metrics are seen in an air shed that has elevated ambient levels of several measured air toxics, such as benzene (CDPHE, 2009; GCPH, 2010).

4.1. Representation of exposures from NGD

It is likely that NGD is the major source of the hydrocarbons observed in the NGD area samples used in this risk assessment. The NGD area monitoring site is located in the midst of multi-acre rural home sites and ranches. Natural gas is the only industry in the area other than agriculture. Furthermore, the site is at least 4 miles upwind from any other major emission source, including Interstate 70 and the town of Silt, Colorado. Interestingly, levels of benzene, m,p-xylene, and 1,3,5-trimethylbenzene measured at this rural monitoring site in 2009 were higher than levels measured at 27 out of 37 EPA air toxics monitoring sites where SNMOCs were measured, including urban sites such as Elizabeth, NJ, Dearborn, MI, and Tulsa, OK (GCPH, 2010; US EPA, 2009b). In addition, the 2007 Garfield County emission inventory attributes the bulk of benzene, xylene, toluene, and ethylbenzene emissions in the county to NGD, with NGD point and non-point sources contributing five times more benzene than any other emission source, including on-road vehicles, wildfires, and wood burning. The emission inventory also indicates that NGD sources (e.g. condensate tanks, drill rigs, venting during completions, fugitive emissions from wells and pipes, and compressor engines) contributed ten times more VOC emissions than any source, other than biogenic sources (e.g. plants, animals, marshes, and the earth) (CDPHE, 2009).

Emissions from flowback operations, which may include emissions from various sources on the pads such as wells and diesel engines, are likely the major source of the hydrocarbons observed in the well completion samples. These samples were collected very near (130 to 500 ft from the center) well pads during uncontrolled flowback into tanks venting directly to the air. As for the NGD area samples, no sources other than those associated with NGD were in the vicinity of the sampling locations.

Subchronic health effects, such as headaches and throat and eye irritation reported by residents during well completion activities

Table 3
Chronic and subchronic reference concentrations, critical effects, and major effects for hydrocarbons in quantitative risk assessment.

Hydrocarbon	Chronic		Subchronic		Critical effect/ target organ	Other effects
	RfC (μg/m³)	Source	RfC (μg/m³)	Source		
1,2,3-Trimethylbenzene	5.00E+00	PPTRV	5.00E+01	PPTRV	Neurological	Respiratory, hematological
1,3,5-Trimethylbenzene	6.00E+00	PPTRV	1.00E+01	PPTRV	Neurological	Hematological
Isopropylbenzene	4.00E+02	IRIS	9.00E+01	HEAST	Renal	Neurological, respiratory
n-Hexane	7.00E+02	IRIS	2.00E+03	PPTRV	Neurological	–
n-Nonane	2.00E+02	PPTRV	2.00E+03	PPTRV	Neurological	Respiratory
n-Pentane	1.00E+03	PPTRV	1.00E+04	PPTRV	Neurological	–
Styrene	1.00E+03	IRIS	3.00E+03	HEAST	Neurological	–
Toluene	5.00E+03	IRIS	5.00E+03	PPTRV	Neurological	Developmental, respiratory
Xylenes, total	1.00E+02	IRIS	4.00E+02	PPTRV	Neurological	Developmental, respiratory
n-propylbenzene	1.00E+03	PPTRV	1.00E+03	Chronic RfC PPTRV	Developmental	Neurological
1,2,4-Trimethylbenzene	7.00E+00	PPTRV	7.00E+01	PPTRV	Decrease in blood clotting time	Neurological, respiratory
1,3-Butadiene	2.00E+00	IRIS	2.00E+00	Chronic RfC IRIS	Reproductive	Neurological, respiratory
Propylene	3.00E+03	CalEPA	1.00E+03	Chronic RfC CalEPA	Respiratory	–
Benzene	3.00E+01	ATSDR	8.00E+01	PPTRV	Decreased lymphocyte count	Neurological, developmental, reproductive
Ethylbenzene	1.00E+03	ATSDR	9.00E+03	PPTRV	Auditory	Neurological, respiratory, renal
Cyclohexane	6.00E+03	IRIS	1.80E+04	PPTRV	Developmental	Neurological
Methylcyclohexane	3.00E+03	HEAST	3.00E+03	HEAST	Renal	–
Aliphatic hydrocarbons C_5–C_8 [a]	6E+02	PPTRV	2.7E+04	PPTRV	Neurological	–
Aliphatic hydrocarbons C_9–C_{18}	1E+02	PPTRV	1E+02	PPTRV	Respiratory	–
Aromatic hydrocarbons C_9–C_{18} [b]	1E+02	PPTRV	1E+03	PPRTV	Decreased maternal body weight	Respiratory

Abbreviations: 95%UCL, 95% upper confidence limit; CalEPA, California Environmental Protection Agency; HEAST, EPA Health Effects Assessment Summary Tables 1997; HQ, hazard quotient; IRIS, Integrated Risk Information System; Max, maximum; PPTRV, EPA Provisional Peer-Reviewed Toxicity Value; RfC, reference concentration; μg/m³, micrograms per cubic meter. Data from CalEPA 2011; IRIS (US EPA, 2011); ORNL 2011.

[a] Based on PPTRV for commercial hexane.

[b] Based on PPTRV for high flash naphtha.

occurring in Garfield County, are consistent with known health effects of many of the hydrocarbons evaluated in this analysis (COGCC, 2011; Witter et al., 2011). Inhalation of trimethylbenzenes and xylenes can irritate the respiratory system and mucous membranes with effects ranging from eye, nose, and throat irritation to difficulty in breathing and impaired lung function (ATSDR, 2007a;

Table 4
Chronic hazard quotients and hazard indices for residents living >½ mile from wells and residents living ≤½ mile from wells.

Hydrocarbon	>½ mile		≤½ mile	
	Chronic HQ based on median concentration	Chronic HQ based on 95% UCL of mean concentration	Chronic HQ based on median concentration	Chronic HQ based on 95% UCL of mean concentration
1,2,3-Trimethylbenzene	2.09E−02	1.90E−02	2.87E−02	5.21E−02
1,2,4-Trimethylbenzene	2.51E−02	4.22E−02	3.64E−02	2.01E−01
1,3,5-Trimethylbenzene	1.96E−02	2.80E−02	3.00E−02	1.99E−01
1,3-Butadiene	5.05E−02	2.23E−02	5.05E−02	2.25E−02
Benzene	3.03E−02	5.40E−02	3.32E−02	8.70E−02
Cyclohexane	3.40E−04	9.98E−04	3.67E−04	1.46E−03
Ethylbenzene	1.63E−04	3.98E−04	1.95E−04	3.23E−03
Isopropylbenzene	3.68E−04	1.78E−04	3.90E−04	3.05E−04
Methylcyclohexane	1.18E−03	2.00E−03	1.36E−03	5.32E−03
n-Hexane	5.49E−03	9.23E−03	5.76E−03	1.47E−02
n-Nonane	2.11E−03	3.14E−03	2.95E−03	2.31E−02
n-Pentane	8.71E−03	1.32E−02	8.79E−03	2.39E−02
n-propylbenzene	9.95E−05	9.59E−05	1.28E−04	2.64E−04
Propylene	1.09E−04	1.27E−04	1.10E−04	1.30E−04
Styrene	1.43E−04	1.25E−04	1.42E−04	4.32E−04
Toluene	3.40E−04	9.28E−04	4.06E−04	1.86E−03
Xylenes, total	1.16E−02	1.57E−02	1.54E−02	1.71E−01
Aliphatic hydrocarbons C_5–C_8	4.63E−02	7.02E−02	4.87E−02	1.36E−01
Aliphatic hydrocarbons C_9–C_{18}	1.22E−02	1.35E−01	1.58E−02	1.83E−01
Aromatic hydrocarbons C_9–C_{18}	5.44E−03	6.67E−03	7.12E−03	2.04E−02
Total Hazard Index	2E−01	4E−01	3E−01	1E+00
Neuorological Effects Hazard Index[a]	2E−01	3E−01	3E−01	9E−01
Respiratory Effects Hazard Index[b]	1E−01	2E−02	2E−02	7E−01
Hematogical Effects Hazard Index[c]	1E−01	1E−01	1E−01	5E−01
Developmental Effects Hazard Index[d]	4E−02	7E−02	5E−02	3E−01

Abbreviations: 95%UCL, 95% upper confidence limit; HQ, hazard quotient.

[a] Sum of HQs for hydrocarbons with neurological effects: 1,2,3-Trimethylbenzene, 1,2,4-Trimethylbenzene, 1,3,5-Trimethylbenzene, 1,3-butadiene, benzene, cyclohexane, ethylbenzene, isopropylbenzene, n-hexane, n-nonane, n-pentane, n-propylbenzene, styrene, toluene, xylenes, aliphatic C_5–C_8 hydrocarbons.

[b] Sum of HQs for hydrocarbons with respiratory effects: 1,2,3-Trimethylbenzene, 1,2,4-Trimethylbenzene, 1,3-butadiene, ethylbenzene, isopropylbenzene, n-nonane, propylene, toluene, xylenes, aliphatic C_9–C_{18} hydrocarbons, aromatic C_9–C_{18} hydrocarbons.

[c] Sum of HQs for hydrocarbons with hematological effects: 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, benzene.

[d] Sum of HQs for hydrocarbons with developmental effects: benzene, cyclohexane, toluene, and xylenes.

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Table 5
Subchronic hazard quotients and hazard indices residents living >½ mile from wells and residents living ≤½ mile from wells.

Hydrocarbon (μg/m^3)	>½ mile		≤½ mile	
	Subchronic HQ based on median concentration	Subchronic HQ based on 95% UCL of mean concentration	Subchronic HQ based on median concentration	Subchronic HQ based on 95% UCL of mean concentration
1,2,3-Trimethylbenzene	2.09E−03	1.90E−03	1.67E−02	6.40E−02
1,2,4-Trimethylbenzene	2.51E−03	4.22E−03	2.38E−02	3.02E−01
1,3,5-Trimethylbenzene	1.18E−02	1.68E−02	1.29E−01	1.95E+00
1,3-Butadiene	5.04E−02	2.23E−02	5.25E−02	8.30E−02
Benzene	1.14E−02	2.02E−02	3.25E−02	2.55E−01
Cyclohexane	1.13E−04	3.33E−04	2.93E−04	3.24E−03
Ethylbenzene	1.81E−05	4.42E−05	8.56E−05	5.96E−03
Isopropylbenzene	1.63E−03	7.92E−04	3.62E−03	1.14E−02
Methylcyclohexane	1.18E−03	2.01E−03	4.67E−03	6.47E−02
n-Hexane	1.92E−03	3.23E−03	3.86E−03	3.98E−02
n-Nonane	2.11E−04	3.14E−04	1.80E−03	3.78E−02
n-Pentane	8.71E−04	1.32E−03	1.05E−03	2.13E−02
n-propylbenzene	9.95E−05	9.57E−05	6.36E−04	3.26E−03
Propylene	1.43E−04	3.80E−04	4.12E−04	6.02E−04
Styrene	5.68E−04	4.16E−05	4.00E−06	1.97E−03
Toluene	4.18E−05	9.28E−04	2.46E−04	1.84E−02
Xylenes, total	2.91E−03	3.93E−03	2.05E−02	7.21E−01
Aliphatic hydrocarbons C_5–C_8	1.07E−03	1.63E−03	2.07E−03	2.89E−02
Aliphatic hydrocarbons C_9–C_{18}	1.3E−02	1.41E−01	7.9E−02	1.03E−00
Aromatic hydrocarbons C_9–C_{18}	6.00E−04	6.95E−04	3.7E−03	2.64E−02
Total Hazard Index	1E−01	2E−01	4E−01	5E+00
Neuorological Effects Hazard Index[a]	9E−02	8E−02	3E−01	4E+00
Respiratory Effects Hazard Index[b]	7E−02	2E−01	2E−01	2E+00
Hematogical Effects Hazard Index[c]	3E−02	4E−02	2E−01	3E+00
Developmental Effects Hazard Index[d]	1E−02	3E−02	5E−02	1E+00

Abbreviations: 95%UCL, 95% upper confidence limit; HQ, hazard quotient.
[a] Sum of HQs for hydrocarbons with neurological effects: 1,2,3-Trimethylbenzene, 1,2,4-Trimethylbenzene, 1,3,5-Trimethylbenzene, 1,3-butadiene, benzene, cyclohexane, ethylbenzene, isopropylbenzene, n-hexane, n-nonane, n-pentane, n-propylbenzene, styrene, toluene, xylenes, aliphatic C_5–C_8 hydrocarbons.
[b] Sum of HQs for hydrocarbons with respiratory effects: 1,2,3-Trimethylbenzene, 1,2,4-Trimethylbenzene, 1,3-butadiene, ethylbenzene, isopropylbenzene, n-nonane, propylene, toluene, xylenes, aliphatic C_9–C_{18} hydrocarbons, aromatic C_9–C_{18} hydrocarbons.
[c] Sum of HQs for hydrocarbons with hematological effects: 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, benzene.
[d] Sum of HQs for hydrocarbons with developmental effects: benzene, cyclohexane, toluene, and xylenes.

ATSDR, 2007b; US EPA, 1994). Inhalation of trimethylbenzenes, xylenes, benzene, and alkanes can adversely affect the nervous system with effects ranging from dizziness, headaches, fatigue at lower exposures to numbness in the limbs, incoordination, tremors, temporary limb paralysis, and unconsciousness at higher exposures (Carpenter et al., 1978; Nilsen et al., 1988; US EPA, 1994; Galvin and Marashi, 1999; ATSDR, 2007a; ATSDR, 2007b).

4.2. Risk assessment as a tool for health impact assessment

HIA is a policy tool used internationally that is being increasingly used in the United States to assess multiple complex hazards and exposures in communities. Comparison of risks between residents based on proximity to wells illustrates how the risk assessment process can be used to support the HIA process. An important component of the HIA process is to identify where and when public health is most likely to be impacted and to recommend mitigations to reduce or eliminate the potential impact (Collins and Koplan, 2009). This risk assessment indicates that public health most likely would be impacted by well completion activities, particularly for residents living nearest the wells. Based on this information, suggested risk prevention strategies in the HIA are directed at minimizing exposures for those living closet to the well pads, especially during well completion activities when emissions are the highest. The HIA includes recommendations to (1) control and monitor emissions during completion transitions and flowback; (2) capture and reduce emissions through use of low or no emission flowback tanks; and (3) establish and maintain communications regarding well pad activities with the community (Witter et al., 2011).

4.3. Comparisons to other risk estimates

This risk assessment is one of the first studies in the peer-reviewed literature to provide a scientific perspective to the potential health risks associated with development of unconventional natural

Table 6
Excess cancer risks for residents living >½ mile from wells and residents living ≤½ mile from wells.

Hydrocarbon	WOE		Unit Risk (μg/m^3)	Source	>½ mile		≤½ mile	
	IRIS	IARC			Cancer risk based on median concentration	Cancer risk based on 95% UCL of mean concentration	Cancer risk based on median concentration	Cancer risk based on 95% UCL of mean concentration
1,3-Butadiene	B2	1	3.00E−05	IRIS	1.30E−06	5.73E−07	1.30E−06	6.54E−07
Benzene	A	1	7.80E−06	IRIS	3.03E−06	5.40E−06	3.33E−06	8.74E−06
Ethylbenzene	NC	2B	2.50E−06	CalEPA	1.75E−07	4.26E−07	2.09E−07	3.48E−06
Styrene	NC	2B	5.00E−07	CEP	3.10E−08	2.70E−08	3.00E−08	9.30E−08
Cumulative cancer risk					5E−06	6E−06	5E−06	1E−05

Abbreviations: 95%UCL, 95% upper confidence limit; CalEPA, California Environmental Protection Agency; CEP, (Caldwell et al., 1998); IARC, International Agency for Research on Cancer; IRIS, Integrated Risk Information System; Max, maximum; NC, not calculated; WOE, weight of evidence; μg/m^3, micrograms per cubic meter. Data from CalEPA 2011; IRIS (US EPA, 2011).

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gas resources. Our results for chronic non-cancer HIs and cancer risks for residents > than ½ mile from wells are similar to those reported for NGD areas in the relatively few previous risk assessments in the non-peer reviewed literature that have addressed this issue (CDPHE, 2010; Coons and Walker, 2008; CDPHE, 2007; Walther, 2011). Our risk assessment differs from these previous risk assessments in that it is the first to separately examine residential populations nearer versus further from wells and to report health impact of emissions resulting from well completions. It also adds information on exposure to air emissions from development of these resources. These data show that it is important to include air pollution in the national dialogue on unconventional NGD that, to date, has largely focused on water exposures to hydraulic fracturing chemicals.

4.4. Limitations

As with all risk assessments, scientific limitations may lead to an over- or underestimation of the actual risks. Factors that may lead to overestimation of risk include use of: 1) 95% UCL on the mean exposure concentrations; 2) maximum detected values for 1,3-butadiene, 2,2,4-trimethylpentane, and styrene because of a low number of detectable measurements; 3) default RME exposure assumptions, such as an exposure time of 24 h per day and exposure frequency of 350 days per year; and 4) upper bound cancer risk and non-cancer toxicity values for some of our major risk drivers. The benzene IUR, for example, is based on the high end of a range of maximum likelihood values and includes uncertainty factors to account for limitations in the epidemiological studies for the dose–response and exposure data (US EPA, 2011). Similiarly, the xylene chronic RfC is adjusted by a factor of 300 to account for uncertainties in extrapolating from animal studies, variability of sensitivity in humans, and extrapolating from subchronic studies (US EPA, 2011). Our use of chronic RfCs values when subchronic RfCs were not available may also have overestimated 1,3-butadiene, n-propylbenzene, and propylene subchronic HQs. None of these three chemicals, however, were primary contributors to the subchronic HI, so their overall effect on the HI is relatively small.

Several factors may have lead to an underestimation of risk in our study results. We were not able to completely characterize exposures because several criteria or hazardous air pollutants directly associated with the NGD process via emissions from wells or equipment used to develop wells, including formaldehyde, acetaldehyde, crotonaldehyde, naphthalene, particulate matter, and polycyclic aromatic hydrocarbons, were not measured. No toxicity values appropriate for quantitative risk assessment were available for assessing the risk to several alkenes and low molecular weight alkanes (particularly $<C_5$ aliphatic hydrocarbons). While at low concentrations the toxicity of alkanes and alkenes is generally considered to be minimal (Sandmeyer, 1981), the maximum concentrations of several low molecular weight alkanes measured in the well completion samples exceeded the 200–1000 $\mu g/m^3$ range of the RfCs for the three alkanes with toxicity values: n-hexane, n-pentane, and n-nonane (US EPA, 2011; ORNL, 2009). We did not consider health effects from acute (i.e., less than 1 h) exposures to peak hydrocarbon emissions because there were no appropriate measurements. Previous risk assessments have estimated an acute HQ of 6 from benzene in grab samples collected when residents noticed odors they attributed to NGD (CDPHE, 2007). We did not include ozone or other potentially relevant exposure pathways such as ingestion of water and inhalation of dust in this risk assessment because of a lack of available data. Elevated concentrations of ozone precursors (specifically, VOCs and nitrogen oxides) have been observed in Garfield County's NGD area and the 8-h average ozone concentration has periodically approached the 75 ppb National Ambient Air Quality Standard (NAAQS) (CDPHE, 2009; GCPH, 2010).

This risk assessment also was limited by the spatial and temporal scope of available monitoring data. For the estimated chronic exposure, we used 3 years of monitoring data to estimate exposures over a 30 year exposure period and a relatively small database of 24 samples collected at varying distances up to 500 ft from a well head (which also were used to estimate shorter-term non-cancer hazard index). Our estimated 20-month subchronic exposure was limited to samples collected in the summer, which may have not have captured temporal variation in well completion emissions. Our ½ mile cut point for defining the two different exposed populations in our exposure scenarios was based on complaint reports from residents living within ½ mile of existing NGD, which were the only data available. The actual distance at which residents may experience greater exposures from air emissions may be less than or greater than a ½ mile, depending on dispersion and local topography and meteorology. This lack of spatially and temporally appropriate data increases the uncertainty associated with the results.

Lastly, this risk assessment was limited in that appropriate data were not available for apportionment to specific sources within NGD (e.g. diesel emissions, the natural gas resource itself, emissions from tanks, etc.). This increases the uncertainty in the potential effectiveness of risk mitigation options.

These limitations and uncertainties in our risk assessment highlight the preliminary nature of our results. However, there is more certainty in the comparison of the risks between the populations and in the comparison of subchronic to chronic exposures because the limitations and uncertainties similarly affected the risk estimates.

4.5. Next steps

Further studies are warranted, in order to reduce the uncertainties in the health effects of exposures to NGD air emissions, to better direct efforts to prevent exposures, and thus address the limitations of this risk assessment. Next steps should include the modeling of short- and longer-term exposures as well as collection of area, residential, and personal exposure data, particularly for peak short-term emissions. Furthermore, studies should examine the toxicity of hydrocarbons, such as alkanes, including health effects of mixtures of HAPs and other air pollutants associated with NGD. Emissions from specific emission sources should be characterized and include development of dispersion profiles of HAPs. This emissions data, when coupled with information on local meteorological conditions and topography, can help provide guidance on minimum distances needed to protect occupant health in nearby homes, schools, and businesses. Studies that incorporate all relevant pathways and exposure scenarios, including occupational exposures, are needed to better understand the impacts of NGD of unconventional resources, such as tight sands and shale, on public health. Prospective medical monitoring and surveillance for potential air pollution-related health effects is needed for populations living in areas near the development of unconventional natural gas resources.

5. Conclusions

Risk assessment can be used as a tool in HIAs to identify where and when public health is most likely to be impacted and to inform risk prevention strategies directed towards efficient reduction of negative health impacts. These preliminary results indicate that health effects resulting from air emissions during development of unconventional natural gas resources are most likely to occur in residents living nearest to the well pads and warrant further study. Risk prevention efforts should be directed towards reducing air emission exposures for persons living and working near wells during well completions.

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ATTACHMENT C

STUDY 9

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

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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.

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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

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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.

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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

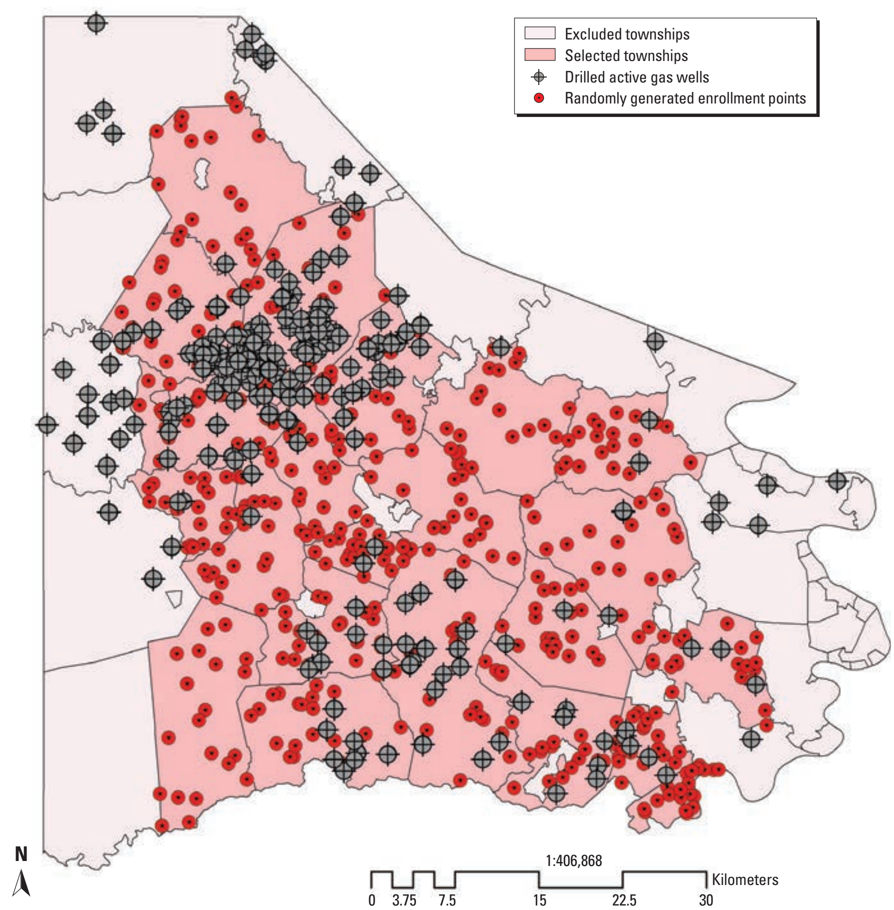

Figure 1. Distribution of drilled active Marcellus Shale natural gas wells (n = 624) and randomly generated sampling sites (n = 760) for eligible municipalities of Washington County, Pennsylvania.

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%; $\chi^2 = 13.8$, $p = 0.001$) (Table 2). Reported upper respiratory symptoms were also more frequent among households < 1 km (39%) compared with households > 2 km from gas wells (18%; $\chi^2 = 17.9$, $p = 0.0001$).

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.

	< 1 km		1–2 km		
Outcome	OR (95% CI)	*p*-Value	OR (95% CI)	*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.

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ATTACHMENT C

STUDY 10

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:

$$\text{IDW well count} = \sum\nolimits_{i=1}^{n} \frac{1}{di} \quad (1),$$

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,

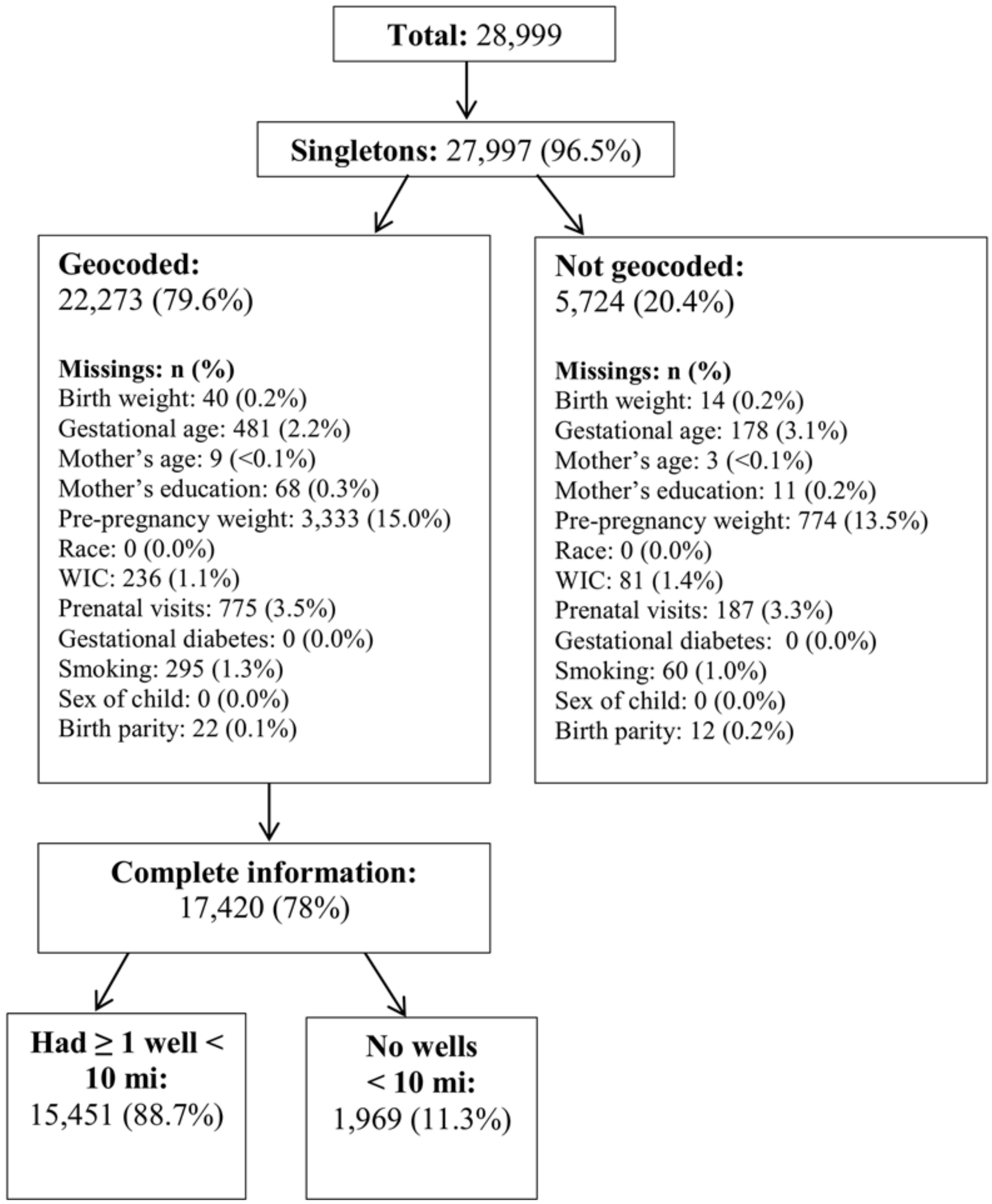

Fig 1. Flowchart of sample sizes and missing data for births in Butler, Washington, and Westmoreland Counties 2007–2010.

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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

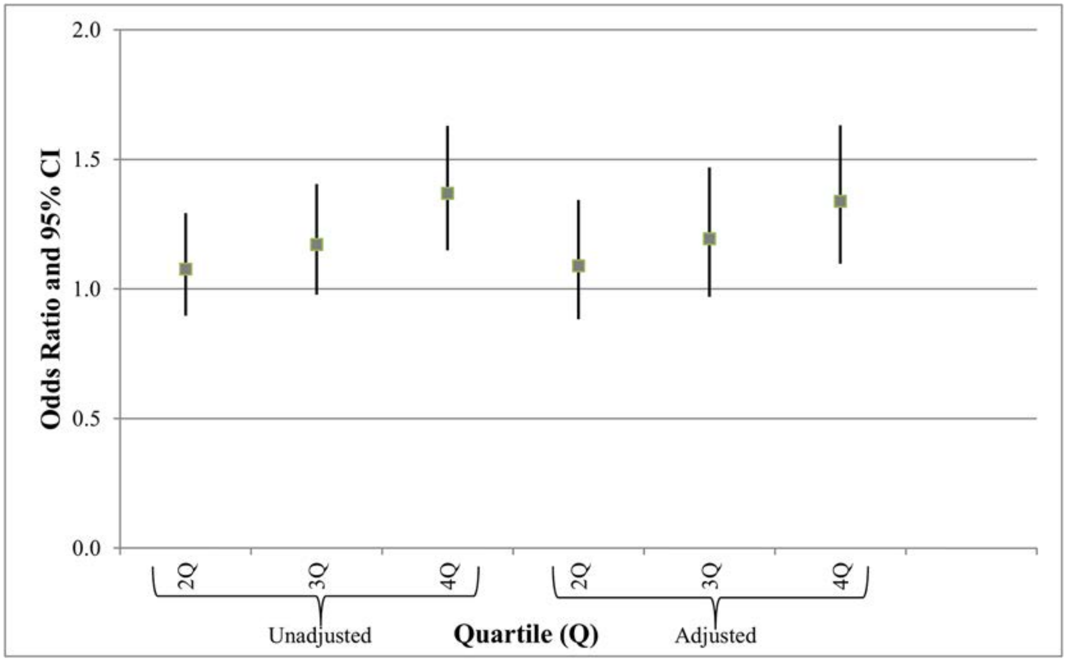

Fig 2. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for small for gestational age (adjusted for mom's age, mom's education, pre-pregnancy weight, gender of infant, prenatal visits, smoking during pregnancy, gestational diabetes, WIC, race, and birth order). Key: Referent (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), $\geq$6.00 wells per mile.

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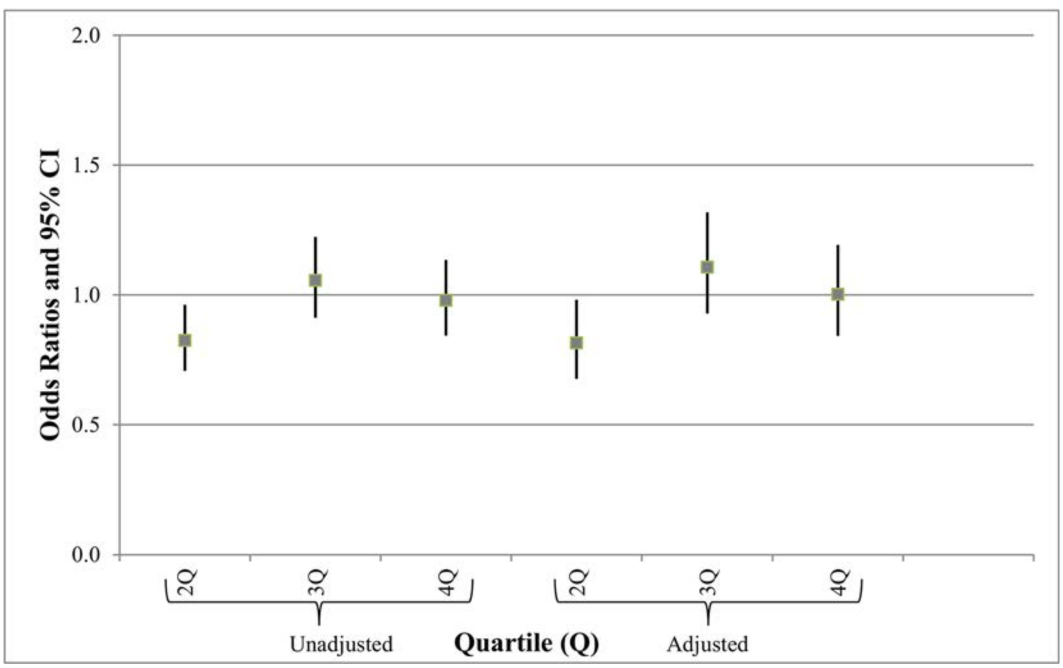

Fig 3. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for prematurity (adjusted for mom's age, mom's education, pre-pregnancy weight, gender of infant, prenatal visits, smoking during pregnancy, gestational diabetes, WIC, race, and birth order). Key: Referent (First quartile),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

STUDY 11

Final Report
For

Pennsylvania Department of Health,
Bureau of Epidemiology

Hydraulic Fracturing Epidemiology Research Studies: Childhood Cancer Case-Control Study

Prepared by:
University of Pittsburgh
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Pennsylvania Department of Health

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Table of Contents

Abbreviations

Abbreviation	Definition
ALL	Acute Lymphocytic Leukemia
ATSDR	Agency for Toxic Substances and Disease Registry
CATI	Computer–Assisted Telephone Interviewing
CHP	Children's Hospital of Pittsburgh
CI	Confidence Intervals
CNS	Central Nervous System
CPDB	Carcinogenic Potency Database
CT	Computed Tomography
EFOT	Ewing Family of Tumor
EPA	US Environmental Protection Agency
GIS	Geographic Information System
HF	Hydraulic Fracturing or fracking
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
IDW	Inverse Distance Weighting
IRB	Institutional Review Board
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NPL	National Priorities List
OR	Odds Ratio
PA	Pennsylvania
PADEP	Pennsylvania Department of Environmental Protection
PADOH	Pennsylvania Department of Health
SEER	Surveillance, Epidemiology, and End Results
SIR	Standard Incidence Ratios
TRI	Toxic Release Inventory
UMTRA	Uranium Mill Tailing Remedial Action
UNGD	Unconventional Natural Gas Development
UV	Ultraviolet
WCS	World Geocoding Service
WHO	World Health Organization

CHILDHOOD CANCER CASE-CONTROL STUDY

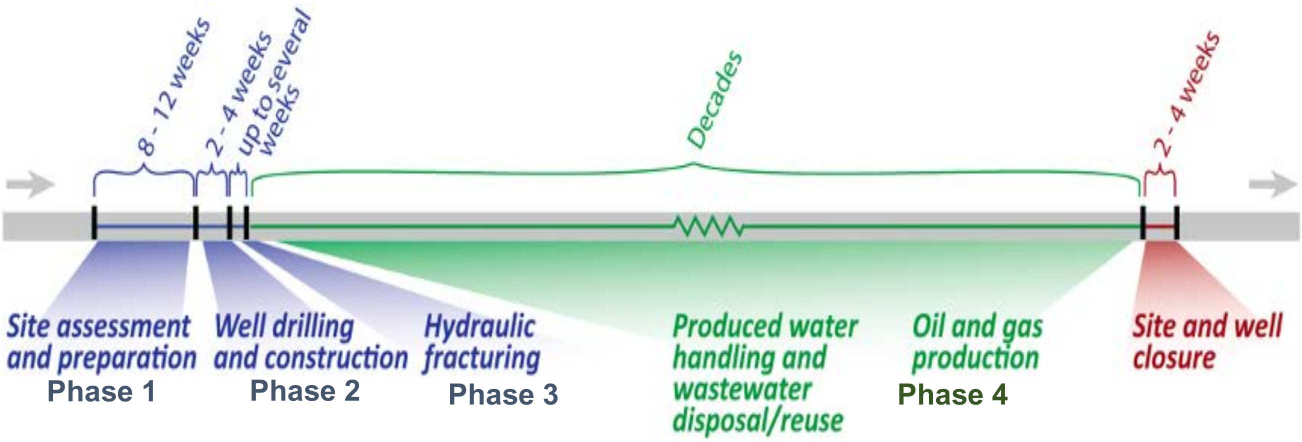
I. Background

Hydraulic fracturing (or fracking) is a type of unconventional natural gas development (UNGD) used to extract natural gas from underground shale rock formations. After obtaining the necessary permits, the first phase of hydraulic fracturing (HF) is well pad preparation. This includes preparing a site for one or more fracturing wells by building access roads and clearing land to build infrastructure. The next phase is drilling in which a borehole is drilled vertically 1 to 2 miles into the ground then turned horizontally into the shale rock (Deziel et al., 2022). Then the steel casing is installed in the borehole and sealed with cement.

Fracturing fluid consists of 90-97% of a base fluid, which is usually water. A fracturing well uses an average of 1.2 million gallons of water. A proppant, usually sand, composes 2-10% of the fracturing fluid. Chemical additives make up less than 2% of the fracturing fluid, though hundreds of chemicals have been reported (Deziel et al., 2022). More information on the chemical additives and their function in fracturing fluid, as well as common constituents reported by the EPA analysis of FracFocus 1.0 (2015) is shown in **Appendix A**. A number of these chemicals include known and suspected endocrine inhibitors and carcinogens (Deziel et al., 2022).

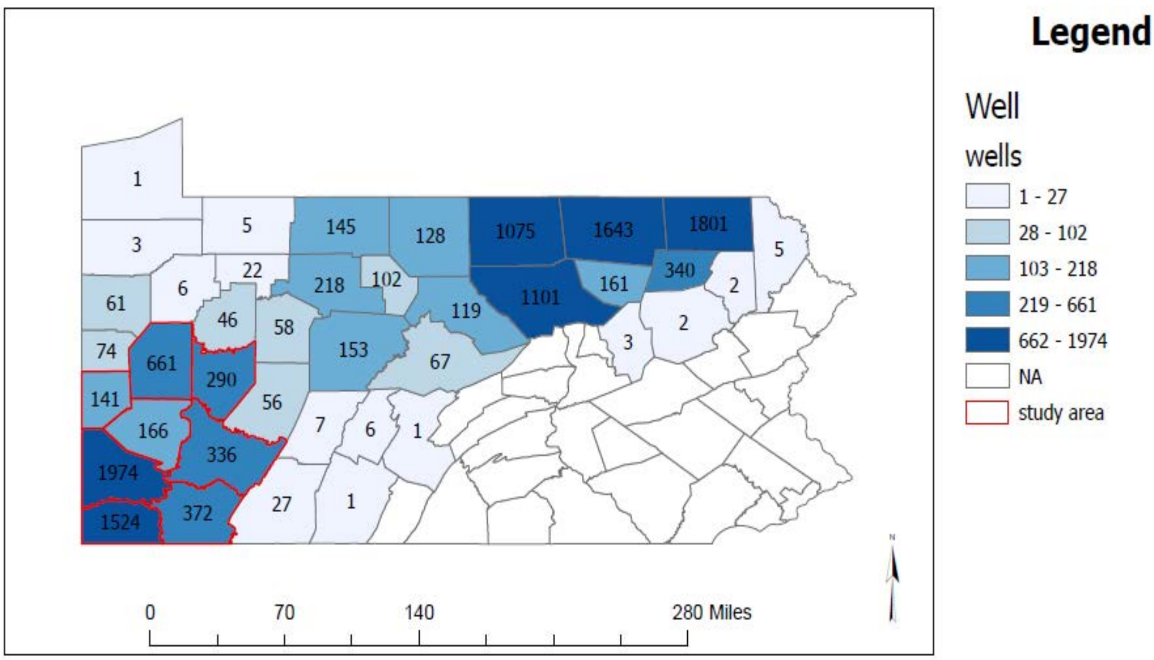
Workers inject this fracturing fluid into the well under high pressure which 'fractures' the rock and releases the natural gas. Once the pressure is released, a mixture of the gas, fracturing fluid, and other compounds found in the rock flow back through the well to the surface. This mixture is often called flowback or produced water. The production phase refers to the separation of the gas from the flowback water, which is then transported through pipelines to a storage facility or processing plant (Deziel et al., 2022). See **Figure 1**.

Figure 1. Hydraulic Fracturing Timeline (Adapted from: U.S. EPA 2016)



The first recorded shale gas well in Pennsylvania was drilled in Erie County in 1860, though modern hydraulic fracturing began in earnest in 2005 in Southwestern Pennsylvania (PA). Currently, Washington County has the largest number of UNGD wells in operation in this region. As of December 2020, there were 12,903 unconventional wells active throughout PA and 5,464 in the 8 county Southwestern PA area. See **Figure 2**. The last county to begin with UNGD drilling was Allegheny County in 2008. The highlighted area on the map includes Allegheny, Armstrong, Beaver, Butler, Fayette, Greene, Washington, and Westmoreland counties, where each had >100 active unconventional oil and natural gas wells in 2020.

Figure 2. Distribution of Wells in Each PA County, with a Total of 12,903 Wells Throughout PA as of December 2020



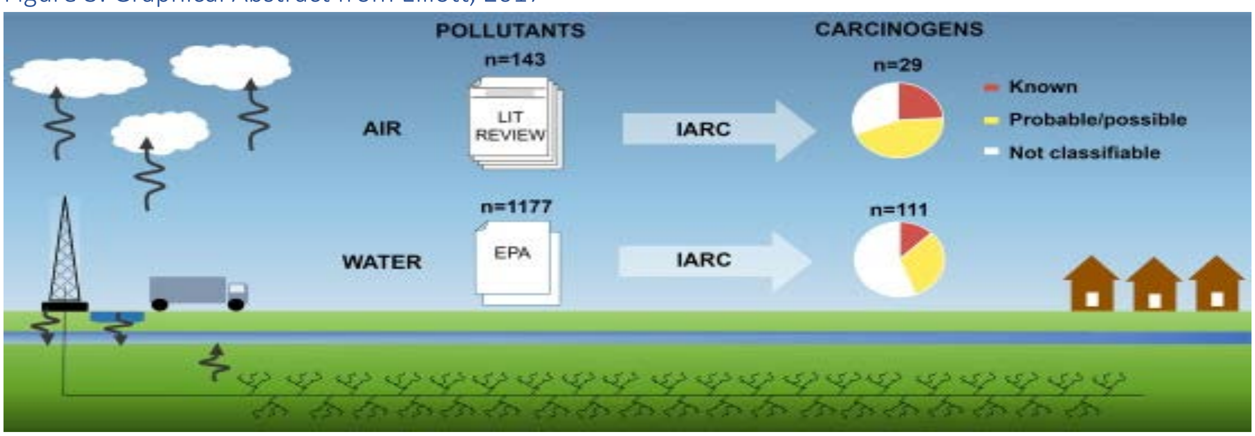
UNGD-related chemicals in the environment

A systematic assessment of carcinogenicity of chemicals in fracturing fluid and flowback water was conducted by Xu et al. (2019). The group assessed 1,173 fracturing fluid-related chemicals identified by the US Environmental Protection Agency (EPA) (Xu et al., 2019). They then linked the fracturing fluid chemical data to the agent classification data from the International Agency for Research on Cancer (IARC) at the World Health Organization (WHO), which was evaluated for human carcinogenic risk. Using IARC's database of 998 chemicals, they found information on 104 fracturing fluid-related chemicals with different evidence in carcinogenicity: 14 were carcinogenic to humans, 7 were probably carcinogenic, and 27 were possibly carcinogenic.

Some of these carcinogenic compounds include 1,3-butadiene, ethanol, ethylene oxide, and formaldehyde, which are found in fracturing fluids; benzo(a)pyrene, beryllium, cadmium, radium-226 and -228 found in flowback; and arsenic, benzene, and chromium (VI) found in both. Additional assessment of the Carcinogenic Potency Database (CPDB) suggested that 66 fracturing fluid-related chemicals are potentially carcinogenic based on rats and mouse models (Xu et al., 2019). Xu et al.'s evaluation suggests that individuals with exposure to certain chemicals in fracturing fluids and wastewater may be at increased risk of cancer, as these chemicals can make their way into ground water and drinking water.

Elliott (2017) also systematically assessed evidence for potential carcinogenicity of both air and water pollutants from hydraulic fracturing exposures but specific to childhood leukemia and lymphoma risk. They likewise evaluated 1,177 chemicals in fracturing fluids and wastewater, finding similar results as those described by Xu et al. They additionally considered 143 UNGD-related air pollutants by review of scientific papers published through 2015 using both PubMed and ProQuest Database, and assessing carcinogenicity evidence of increased risk of leukemia and lymphoma from these chemicals using the IARC monographs. See **Figure 3**.

Figure 3: Graphical Abstract from Elliott, 2017



Of 143 potential air pollutants, 29 (20%) have been evaluated for carcinogenicity by IARC and the remaining 114 (80%) have not been evaluated (Elliot, 2017). Of the 29 air pollutants evaluated, 7 (24%) were carcinogenic to humans, 2 (7%) were considered probably carcinogenic to humans, 11 (38%) were considered possibly carcinogenic to humans, and the remaining 9 (31%) could not be classified with respect to their carcinogenicity. Of the 20 known, probable, or possible carcinogens, there has been supporting evidence for 11 air pollutants that were associated with an increased risk of leukemia or lymphoma. These included 5 known human carcinogens (1,3-butadiene, benzene, ethanol, formaldehyde, diesel engine exhaust), 2 probable human carcinogens (dibenz[*a,h*]anthracene, tetrachloroethylene), and 4 possible human carcinogens (carbon tetrachloroethylene, chrysene, indenol[1,2,3-*cd] pyrene* and styrene).

Risk Factors for Childhood Cancer

Although cancer in children and adolescents is rare, it is the leading cause of death by disease past infancy among children in the United States, according to the National Cancer Institute (NCI, 2021).

In 2021, it was estimated that 15,590 children and adolescents ages 0 to 19 were diagnosed with cancer and 1,780 died of the disease in the United States (Siegel, 2021). Overall, among children and adolescents (ages 0 to 19) in the United States, the most common types of cancer are leukemias, brain and central nervous system (CNS) tumors, and lymphomas (NCI, 2021). These are also the types of cancers found to be associated with various environmental exposures in both adults and children in the literature (NCI, 2021).

Many childhood cancers are caused by genetic mutations that increase cancer risk. Germline alterations (or variants) associated with an increased risk of cancer can be passed down from parents to their offspring, or somatic mutations in cells can occur spontaneously in cells during development (NCI, 2021). About 6-8% of all cancers in children are caused by an inherited pathogenic variant (harmful alteration) in a cancer predisposition gene (Gröbner et al., 2018, Zhang et al., 2015). For example, children with Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Fanconi anemia, Noonan syndrome, and von Hippel-Lindau syndrome, have an increased risk of childhood cancer.

Genomic changes that arise during development of one of the germ cells (sperm or egg) which unite to form the zygote that becomes a child can increase the risk of cancer in that child (NCI, 2021). Genomic changes can include broken, missing, rearranged, or extra chromosomes and gene variants. One such alteration is trisomy 21, or the presence of an extra copy of chromosome 21, which causes Down syndrome. Children with Down syndrome are 10 to 20 times more likely to develop leukemia than children without Down syndrome (Ross, 2005). However, only a small proportion of childhood leukemia is linked to Down syndrome (NCI, 2021).

Genetic changes associated with cancer can also occur in different cells of the body after birth, as the body is actively growing and developing during early childhood (Moore et al., 2021). The extent to which these changes react to environmental exposures is unclear. In adults, exposure to cancer-causing substances in the environment, such as cigarette smoke, asbestos, and ultraviolet (UV) radiation from the sun is known to cause genetic changes that can lead to cancer (NCI, 2021). However, environmental causes of childhood cancer have been particularly difficult to identify, this is partly because cancer in children is rare and because it is difficult to determine what children may have been exposed to early in their development (NCI, 2021).

Nevertheless, several environmental exposures, such as ionizing radiation, can lead to the development of leukemia and other cancers in children and adolescents (NCI, 2021). Children and adolescents who were exposed to radiation from the atomic bombs dropped in Japan during the Second World War had an elevated risk of leukemia (Hsu et al., 2013). Also, children exposed to radiation from the Chernobyl nuclear plant accident had an elevated risk for thyroid cancer (Cardis, 2011).

Exposure of parents to ionizing radiation is also a concern in terms of the development of cancer in their future offspring. Exposure to diagnostic medical radiation from computed tomography (CT) scans by children whose mothers had x-rays during pregnancy (that is, children who were exposed before birth) and children exposed after birth has been linked to a slight increase in risk of leukemia and brain tumors, and possibly other cancers (Pearce et al., 2012). However, genomic analysis of children born to people exposed to radiation at Chernobyl indicates that this exposure did not lead to an increase in new genetic changes passed from parent to child (Yeager et al., 2021).

Several other environmental exposures have also been associated with childhood cancer; however, it is difficult to draw firm conclusions because of challenges in studying these exposures. For some types of childhood leukemia (particularly acute lymphoblastic leukemia), researchers have identified associations with paternal tobacco smoking (Liu, 2011, Cao, 2020); exposure to certain pesticides used in and around the home (Bailey et al., 2015) or by parents at their workplaces (Van Maele-Fabry, 2010, Vinson, 2011); use of solvents, organic chemicals found in some household products; and outdoor air pollution (NCI, 2021).

Investigations of childhood brain tumors and leukemia and lymphomas have studied associations with exposures to pesticides in and around the home. A meta-analysis of 277 studies found an increased risk of leukemia and lymphomas in children exposed to indoor residential pesticides. A significant increase in the odds of leukemia was also associated with herbicide exposure. Also observed was a positive but not statistically significant association between childhood home pesticide or herbicide exposure and childhood brain tumors. (Chen et al., 2015). Johnson et al, 2014 reported an association of maternal consumption of cured meats and childhood brain tumors. A recent study (Lombardi et al, 2021) used the California cancer registry to identify childhood cases of brain tumors and linked residence to agricultural pesticide exposure. They noted a significant increased risk of CNS tumors and proximity to residences.

Researchers have also identified factors that may be associated with reduced risk of childhood cancer (NCI, 2021). For example, maternal consumption of folate has been associated with reduced risks of both leukemia and brain tumors in children (Chiavarini, 2018). Also, being breastfed and having been exposed to routine childhood infections are both associated with a lowered risk of developing childhood leukemia (Amitay, 2015).

Previous Hydraulic Fracturing and Childhood Cancer Studies

Three studies have been published that examined a possible association between hydraulic fracturing and the risk of childhood cancer. The study populations and main findings are briefly summarized in **Table 1.** Below are more details for each of these three studies.

Fryzek et al. (2013) were the first to investigate a potential relationship between childhood cancer and hydraulic fracturing in Pennsylvania. The study compared cancer incidence rates at the county level before and after hydraulic fracturing to determine if rates increased. The study did not find a significant increase in the incidence of total cancers or leukemia. It did find a slightly elevated incidence rate for central nervous tumors after drilling began. The ecological study design employed has major limitations due to a lack of individual level data. Further studies were required to draw solid conclusions about the relationship between hydraulic fracturing and childhood cancer.

Table 1: Comparison of Previous HF and Peer-Reviewed Childhood Cancer Studies

	Fryzek et al., 2013	**McKenzie et al., 2017**	**Clark et al. 2022**
Study area	Pennsylvania	Rural Colorado	Pennsylvania
Time period	1990-2009 (stopped data collection 2 years after hydraulic fracturing began - latency issues)	2001-2013	2009-2017
Study population size/design	Standardized incidence rates by county for cases of CNS and leukemia, age 0-20 (N =1,874)	Case-control: aged 0-24, Final sample: 87 ALL, 50 lymphoma and 528 controls diagnosed with non-hematologic cancer sample	Case-control study, N=405 cases of ALL and 2,080 controls
Data source	PA Cancer Registry, US Census Bureau	Colorado Central Cancer Registry	PA Cancer Registry, PA Vital Records (Bureau of Health Statistics and Registries)
Exposure metrics	Compared SIRs before and after drilling using spud dates (date drilling operations begin)	Inverse distance weighted oil and gas well counts within a 16.1 km radius of the residence at time of diagnosis	Inverse distance-squared weighted well counts with buffer sizes 2, 5, and 10 km from birth address for the association between residential proximity to UNGD and ALL in primary exposure and perinatal window
Outcome	Childhood cancer, childhood leukemia, and CNS tumors	ALL and NHL	ALL
Results	1. The observed number of childhood cancers both before and after drilling were as expected (based on SEER cancer incidence rates) 2. **No evidence** that persons living in counties with HF experienced higher childhood cancer rates overall or for childhood leukemia	1. Children aged 0-24 years diagnosed with NHL were **no more likely** to live in areas with active oil and gas development than children diagnosed with non-hematologic cancer 2. Children aged 5-24 years diagnosed with ALL were **more likely** than children diagnosed with non-hematologic cancer to live within 16.1-km of an active oil and gas well	1. Children with at least one UNGD well within 2 km of their birth residence during the primary window had *1.98 (95% CI: 1.06, 3.69) times* the odds of developing ALL in comparison with those with no UNGD wells 2. Children with at least one vs. no UNGD wells within 2 km during the perinatal window had *2.80 (95% CI: 1.11, 7.05) times the odds of developing* ALL

Two case-control studies have been published in the US involving individual data on childhood cancer risk and hydraulic fracturing. The first was conducted between 2001-2013 in Colorado by McKenzie et al. (2017); and the other was conducted between 2009-2017 in Pennsylvania by Clark et al. (2022).

McKenzie et al. (2017) conducted a case-control study in rural Colorado and included participants who were 0-24 years old and diagnosed with cancer between 2001-2013. For each child, they estimated exposure to hydraulic fracturing activity by calculating the distance between the participants' residences and oil and gas wells within a ten-mile radius. Exposure metrics accounted for both the density and proximity of wells to the child. The logistic regression utilized adjusted for age, race, gender, income, and elevation.

Children aged 0-24 with acute lymphoblastic leukemia (ALL) were more likely to live in areas with active wells. For ages 5-24, ALL cases were 4.3 times as likely to be in the highest exposure category. Further adjustment for year of diagnosis increased the association. The study's limitations included the use of non-hematologic cancer cases as a control group, the substantial number of cancer cases that could not be geocoded (28%), and the sole use of residence at cancer diagnosis to calculate exposure, which is not static and can result in misclassification bias.

A more recent case-control study was reported by Clark et al. (2022), which included 405 children aged 2-7 diagnosed with ALL in Pennsylvania between 2009–2017, and 2,080 controls matched on birth year. They calculated a similar exposure metric to the McKenzie study (2017) but used different distance cutoffs to better understand how distance affects exposure levels. They investigated two time-based exposure windows: a primary window (3 months preconception to 1 year prior to diagnosis/index date) and a perinatal window (3 months preconception to birth).

Clark et al. used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (Cis) for the association between residential proximity to UNGD and ALL in two exposure windows. Children with at least one UNGD well within 2 km (1.2 mile) of their birth residence during the primary window had 1.98 times the odds of developing ALL in comparison with those with no UNGD wells (95% CI: 1.06, 3.69). This result was only based on 7 cases. After adjusting for maternal race and other potential confounders, the OR was no longer statistically significant (OR=1.74, 95% CI: 0.93, 3.27). Similar ORs were produced by models using the water pathway-specific metric.

A major limitation of the Clark et al. study was that a considerable proportion (93-98%) of the study population had no exposure to any UNGD activity within a 10-mile radius. Regulations in metropolitan areas such as Philadelphia and Pittsburgh, or the lack of shale deposits, prohibit hydraulic fracturing activity in sizable portions of Pennsylvania. High proportions of unexposed participants within the study hindered the investigators' ability to identify associations.

In addition to the three peer-reviewed studies, on February 13, 2019, the Pittsburgh-based TV news channel WPXI aired a story regarding a potential cluster of Ewing sarcoma, also sometimes called the Ewing family of tumors (EFOT), a specific type of bone or soft tissue cancer usually occurring in childhood or adolescence. Subsequently, the PA Department of Health received many calls concerning multiple children in the Canon-McMillan School District in Washington County, reporting that they had been diagnosed with EFOT. Several parents came forward to say that their children were also diagnosed with the same disease.

This prompted a cancer incidence survey reported on April 22, 2019 (PADOH, 2019). The PA Department of Health analyzed cancer registry data in three time periods: 1985−1994, 1995−2004 and 2005−2017. These three time periods were used to assess cancer incidence trends over time. This analysis used the mid-time period census population (1990, 2000, and 2010 census data) for age adjustment. Age-standardized SIRs for various childhood cancer types and their 95% CIs for Washington County and Canon-McMillan School District residents were calculated respectively by gender to determine whether the residents experienced a significant excess of cancer incidence compared to the rest of the Pennsylvania population.

Study results for Canon-McMillan School District and incidence of EFOT indicated that there were no cases reported during the first two time periods before hydraulic fracturing. However, there were three cases reported during the 2005-2017 period, which coincided with hydraulic fracturing. The SIRs of Ewing sarcoma estimated based on this small number of cases were considered unstable and difficult to interpret. Overall, total childhood cancer incidence rates were also calculated, and both female and male childhood cancer rates were not appreciably different from the rest of the Commonwealth during any of the three time periods. Moreover, childhood cancer rates in the school district decreased over the last two time periods. The PADOH, however, stated that it would continue to closely monitor EFOT and pediatric cancer incidence in Pennsylvania over the next several years as new data becomes available through the PA cancer registry.

Community concerns persisted, prompting a supplemental analysis reported in March 2020 in addition to advancing other research studies. The present case-control study was initiated by PA Governor Wolf’s administration due to concerns about the Ewing sarcoma cluster and a significant rise in hydraulic fracturing and UNGD drilling in western PA since 2005.

Study Aims and Objectives

This study aims to investigate the risk for childhood cancer related to environmental exposures from UNGD hydraulic fracturing in Southwestern Pennsylvania.

Objectives:

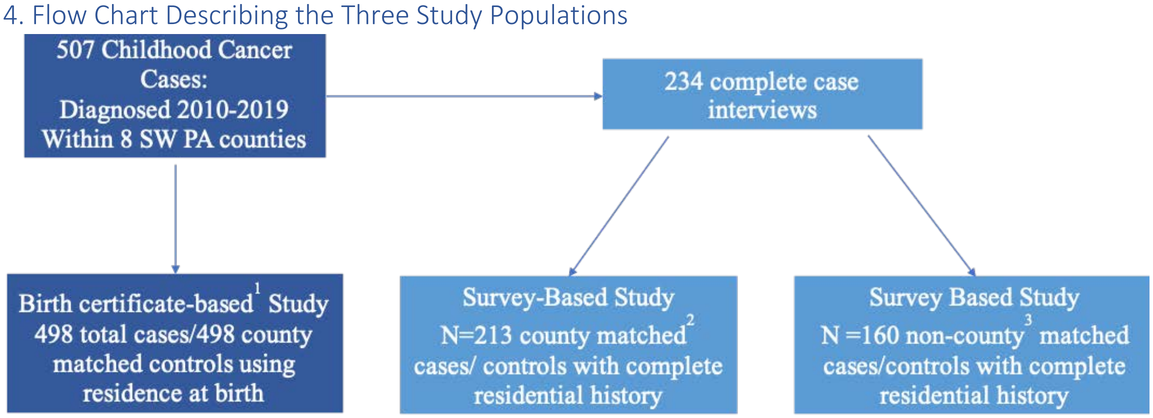
1) We built upon previous studies of exposure to hydraulic fracturing and risk of childhood cancer by conducting a matched case control study using the entire sample of cancer cases identified within the 8-county study area and identifying one randomly selected age, gender, race, and county matched control. Birth records were used to extract information on the mother's and newborn's residence and their characteristics. This birth record-based /cancer registry study enabled comparison with earlier studies conducted by McKenzie (2017) and Clark (2022).

2) An overall UNGD well activity metric was created using each of the individual phases to investigate the childhood cancer risk while controlling for sociodemographic, health history, and behaviors in the year before birth up to the child's cancer diagnosis date.

3) This study also sought to collect more detailed residential histories that can be applied to individual phases and overall UNGD well activity in childhood cancer cases and controls.

Study Design: The study examined three populations derived from the 507 childhood cancer cases diagnosed from 2010-2019 in the eight-county Southwestern Pennsylvania area. The study team completed 234 residency interviews for cases and were able to match 213 of these cases with controls born in the same county, and 160 with controls born in different counties (but still in the eight-county area). Of the total of 507 childhood Cancer Cases, a total of 498 cases were matched to a new group of county-matched controls using only birth certificate data. Nine cases were removed from the full list of cases during data verification.

Figure 4. Flow Chart Describing the Three Study Populations



1. Birth certificate-based means the exposure is based on the mother's residence at birth.
2. County-matched means controls came from the same county as the case.
3. Non-county-matched means controls were chosen at random from the eight-county area.

II. Methods

Study Population

All cases and controls were born in one of the eight counties selected for this study, including Allegheny County (except city of Pittsburgh), Armstrong, Beaver, Butler, Fayette, Greene, Washington, and Westmoreland. Case children were diagnosed with any of four types of malignancies described below and had an address within the defined study area at the time of cancer diagnosis between the years of 2010-2019.

Due to restrictions in hydraulic fracturing within city limits of Pittsburgh, it was necessary to exclude any cases or controls whose parents lived in a zip code located in, or part of, the City of Pittsburgh, as indicated on the birth record or at time of cancer diagnosis. Zip codes excluded from the City of Pittsburgh are shown in **Appendix B.**

Case Inclusion Criteria

All cases of childhood cancer in the present study were identified through the PA Cancer Registry diagnosed from 2010-2019. The cancer types were leukemia, lymphoma, CNS tumors, and malignant bone tumors diagnosed at 0-19 years of age. We extended the age range up to 29 years for malignant bone tumors, including EFOT, to increase sample size due to the rarity of the condition and its later presentation. These specific malignancy types were defined according to the International Classification of Childhood Cancer Recode Third Edition (ICD-O-03/IARC 2017), which is recommended by the NCI Surveillance, Epidemiology, and End Results (SEER) Program. See **Table 2**.

Table 2. Definition of Childhood Cancer Cases for the Case-Control Study in Western PA (International Classification of Childhood Cancer Recode Third Edition, ICD-O-3/IARC 2017)

Cancer type	ICCC Recode 3rd ICD-O-3/ IARC 2017 morphology codes	Behavior codes	ICD-O-3 primary site code
I. Leukemias, Myeloproliferative, and Myelodysplastic Diseases (0-19 years of age)			
1. Precursor cell leukemia	9811-9818, 9837	3	C420, C421, C423, C424, C809
	9835, 9836	3	C000-C809
2.Mature B-cell leukemias	9823	3	C420, C421, C423, C424, C809
	9826, 9832, 9833, 9940	3	C000-C809
3. Mature T-cell and Natural Killer (NK) cell leukemias	9827	3	C420, C421, C423, C424, C809
	9831, 9834, 9948	3	C000-C809
4. Lymphoid leukemia, NOS	9591	3	C420, C421, C423, C424
	9820	3	C000-C809
5. Acute myeloid leukemias	9840, 9861, 9865-9867, 9869-9874, 9891, 9895-9897, 9898, 9910, 9911, 9920, 9930, 9931	3	C000-C809
6. Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	3	C000-C809
7. Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989, 9991, 9992	3	C000-C809
8. Unspecified and other specified leukemias	9800, 9801, 9805-9809, 9860, 9965-9967	3	C000-C809
II. Lymphoma (0-19 years of age)			
1. Precursor cell lymphomas	9727-9729	3	C000-C809
	9811-9818, 9837	3	C000-C419, C422, C440-C779
2. Mature B-cell lymphomas (except Burkitt lymphoma)	9597, 9670, 9671, 9673, 9675, 9678-9680, 9684, 9688-9691, 9695, 9698, 9699, 9712, 9731-9735, 9737, 9738, 9761, 9762, 9764-9766, 9769, 9970, 9971	3	C000-C809
	9823	3	C000-C419, C422, C440-C779
3. Mature T-cell and NK-cell lymphomas	9700-9702, 9705, 9708, 9709, 9714, 9716-9719, 9724-9726, 9767, 9768	3	C000-C809
	9827	3	C000-C419, C422, C440-C779
4. non-Hodgkin lymphomas, NOS	9591	3	C000-C419, C422, C440-C779, C809
	9760	3	C000-C809
5. Burkitt lymphoma	9687	3	C000-C809
6. Miscellaneous lymphoreticular neoplasms	9740-9742, 9750, 9751, 9754-9759	3	C000-C809
7. Unspecified lymphomas	9590, 9596	3	C000-C809

Table 2 Continued. Definition of Childhood Cancer Cases for the Case-Control Study in Western PA (International Classification of Childhood Cancer Recode Third Edition, ICD-O-3/IARC 2017)

Cancer type	ICCC Recode 3rd ICD-O-3 IARC 2017 morphology codes	Behavior codes	ICD-O-3 primary site code
III. CNS and Miscellaneous Intracranial and Intraspinal Neoplasms (0-19 years of age)			
1. Ependymomas and choroid plexus tumor	9383, 9390, 9391-9394, 9396	0-1, 3	C000-C809
2. Astrocytomas	9380	0-1, 3	C723
	9384, 9400-9411, 9420-9424, 9425, 9440-9442	0-1, 3	C000-C809
3. Intracranial and intraspinal embryonal tumors	9470-9478, 9480, 9508	0-1, 3	C000-C809
	9501-9504	0-1, 3	C700-C729
4. Other gliomas	9381, 9382, 9385, 9430, 9431, 9444, 9445, 9450, 9451, 9460	0-1, 3	C000-C809
	9380	0-1, 3	C700-C722, C724-C729, C751, C753
5. Other specified intracranial and intraspinal neoplasms	9840, 9861, 9865-9867, 9869-9874, 9891, 9895-9897, 9898, 9910, 9911, 9920, 9930, 9931	3	C000-C809
	8158, 8290	0-1, 3	C751
6. Unspecified intracranial and intraspinal neoplasms	8000-8005	0-1, 3	C700-C729, C751-C753
IV. Malignant Bone Tumor (0-29 years)			
1. Osteosarcoma	9180–9187, 9191–9195, 9200	3	C400-C419, C760-C768, C809
2. Chondrosarcomas	9210, 9220, 9240	3	C400-C419, C760-C768, C809
	9211-9213, 9221, 9222, 9230, 9241-9243		C000-C809
	9231		C400-C419
3. Ewing tumor and related sarcomas of bone	9260	3	C400-C419, C760-C768, C809
	9365		C000-C809
	9364		C000-C809
4.. Other specified malignant bone tumors	8810, 8811, 8818, 8823, 8830	3	C400-C419
	8812, 9262, 9370-9372, 9270-9275, 9280-9282, 9290, 9300-9302, 9310-9312, 9320-9322, 9330, 9340-9342, 9250, 9261		C000-C809
5. Unspecified malignant bone tumors	8000-8005, 8800, 8801, 8803-8805	3	C400-C419

Exclusion of Ineligible Cases

A total of 593 cancer cases were identified from the PA Cancer Registry between 2010-2019 according to the case eligibility criteria described above. During the data checking and cleaning process, the study team identified the following number of cancer cases were ineligible, and thus were excluded from the final statistical analysis:

- 41 based on the Third Edition ICD-O-3/IARC 2017
- 25 diagnosed within the City of Pittsburgh
- 20 born outside of the eight-county study area.

After these cases were excluded, a total of 507 cancer cases were deemed eligible for the study.

Control Selection

We referenced the birth record registry at PA Bureau of Health Statistics and Registries to select age-, sex- and race-matched controls for either the county-matched or non-county-matched groups. The details of the specific control selection algorithm are provided in Appendix B of this report.

The following steps were followed to obtain a county-matched control:

- A control was selected among children whose mother's residence was recorded on the birth record in the same county as the index case at birth.
- In addition to age, sex, and race, a control without matching on county was selected among children whose mother's residence was within the eight counties of the study area.
- Eligible controls were born within ± 45 days of the index case and were of the same sex and mother's race. For each case, up to 40 county-matched controls and 40 non-county-matched controls were randomly chosen by the PADOH without replacement.
- If the number of eligible controls was fewer than 40 for a given index case, the PA Bureau of Health Statistics and Registries provided information on all eligible controls.
- If a control was matched to multiple cases, a simple random sampling algorithm without replacement was used to determine the matched index case.

We made attempts to locate and update the information of current and past residence history of all cases and 20 of the 40 eligible controls (due to time limitations) through the contact information tracing service Lexis Nexis (described in detail below). Additionally, we used Spokeo, an online tracing service that provides property records, emails, addresses, and phone numbers to confirm residential history and contact information when needed. A unique random number was generated during the control selection process for each of 40 eligible controls per case.

The county-matched control was chosen to help adjust for both urban/rural differences within each county and to assure the greatest similarity of sociodemographic and environmental characteristics to the index cancer case. The non-county match was chosen to limit potential bias from over-matching. The duration of the exposure data collected for the control subject was the same as for the index case, and personal history was obtained up to the index date, which was defined as the date of cancer diagnosis for cases. The same date was applied to matched controls.

Survey

A survey questionnaire was developed based on an ATSDR (Agency for Toxic Substances and Disease Registry) childhood cancer cluster investigation (State of New Jersey Department of Health, 2017) and was modified to include hydraulic fracturing, and industrial and farming activity with an emphasis on residential history. The objective of the survey was to capture the mother's and child's environmental exposure history, residential history, sociodemographic information, health history, and behaviors in the year prior to birth up to the cancer diagnosis date. The survey was then uploaded to a Qualtrics (Provo, UT) software platform. If there were any questions the parent was uncomfortable addressing, they could decline to answer at any time. See **Appendix D**.

As will be described below, the initial response rate from the PADOH recruitment brochure was low (20%) and it was determined that the at least 45 minutes needed to answer the survey questions was negatively affecting the response rate. It became necessary to shorten the questionnaire into a more user-friendly online version, which could be taken at any time. The revised survey included many of the same sections but included fewer questions. See **Table 3**.

Table 3. Main Sections of Case-control Survey

1. Parental background and demographics	5. Maternal reproductive history
2. Residential history, home characteristics, and environmental risk factors for all addresses	6. Maternal medical procedures that occurred during pregnancy with case/control child
3. Occupational and lifestyle histories of the parent(s)	7. Child's medical procedure and infection history
4. Familial cancer history	8. Optional questions regarding household income, interest in future studies, opportunity to share any additional relevant information

The shortened survey is included in **Appendix D**. The longer survey is available upon request.

Overview of Recruitment and Enrollment Process

The Institutional Review Board (IRB)/consent application for this study (protocol number 21020141) was approved by the University of Pittsburgh IRB on March 16, 2021. The PADOH-specific IRB application was approved on June 17, 2021. The University of Pittsburgh applied for and was granted access to protected health information in a data sharing agreement from the PADOH on April 19, and July 7, 2021, respectively. Parents of case and control children, not the children themselves, were asked to participate in the study. The information collected included residence of the mother, and both parents' occupation and health behaviors, including the pregnancy period and early years of the child's life. There was no assent process for children under 18. IRB materials, the timeline of study events, and outreach and recruitment materials are included in **Appendix C**.

PADOH leadership strongly recommended a government-approved third-party tracing agency, LexisNexis, to provide updated and confirmed contact information for recruitment mailings, phone calls, text messages, and emails. The LexisNexis contract was finalized in August 2021, and updated contact information was provided in September 2021, prior to the dissemination of the first round of case recruitment mailings. The initial case dataset was received from the PADOH in September 2021, with the decedent cases received in April 2022.

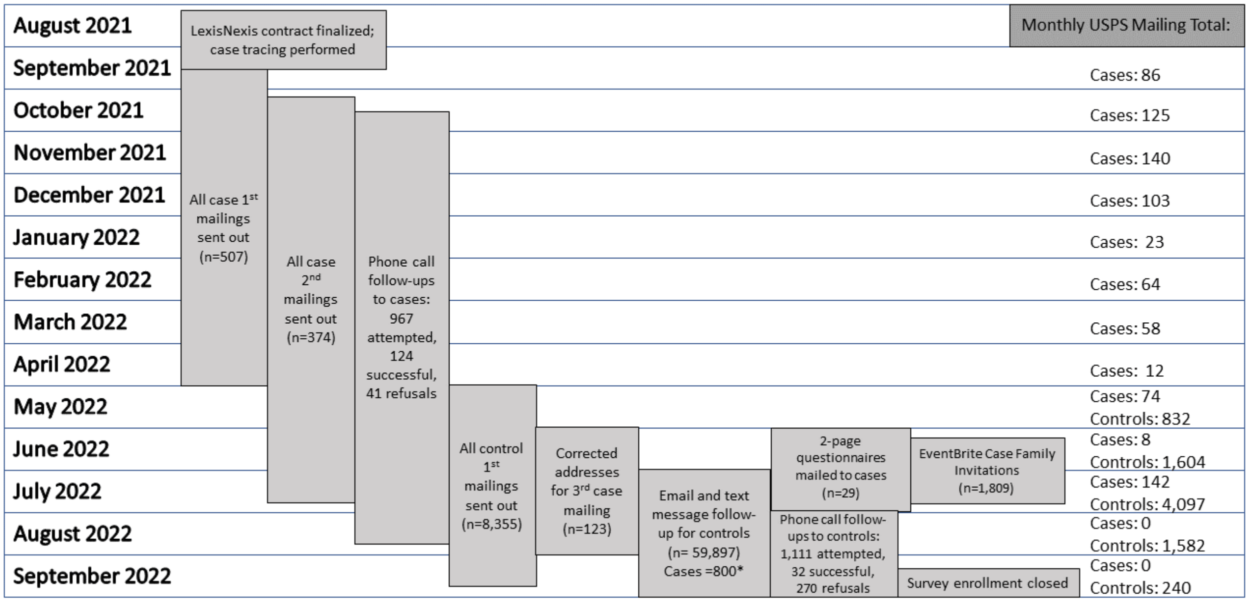
The initial case recruitment protocol, beginning in late September 2021, included a letter from the PADOH Secretary of Health inviting families to schedule a 45–60-minute telephone interview, a brochure explaining the study, and an opt-in/opt-out card with a pre-addressed return envelope. The study team's strategy was to prioritize case recruitment given the need for a sample of controls matched on age, race, gender, and county. Participants who did not respond were sent an additional letter.

Telephone interviewers attempted to contact all parents who opted in using a computer–assisted telephone interviewing (CATI) system to manage sample and call attempts. The CATI system was linked to a Qualtrics-based survey which interviewers used to administer the survey instrument. The PADOH protected-access protocol mandated that only one phone call be made to request participation after receipt of the two recruitment mailings.

Due to concern about the initial low response rate (<20%) after the two letters were sent and follow-up calls were made, the study team initiated a briefer questionnaire that included an online 20–25-minute interview facilitated by co-investigator Dr. Todd Bear and the Population Survey Facility in Pitt School of Medicine in March 2022. In addition, in May 2022 the survey team initiated a shortened two-page residential questionnaire that captured a complete residential history. See **Figure 5** for a timeline of recruitment efforts.

To augment the study response rate and enhance communication with families, the study team solicited support from Dr. Jean Tersak, of UPMC Children's Hospital of Pittsburgh, who provided a letter of support for the study which was subsequently included in all study recruitment mailings. Dr. Tersak was added as a study co-investigator in June 2022.

Figure 5. Timeline of Recruitment Efforts for Cases and Controls



*in follow-up of phone calls

In summer 2022, the study team worked with community nurses and supervisors at state health centers in Washington and Westmoreland counties to facilitate in-person informational sessions at respective health centers in Washington and Greensburg. The goal of these planned sessions was to make the study team available to answer any questions the invited case families may have had regarding the study and their invitation to participate, as well as to facilitate their participation. The study team utilized the email addresses provided by LexisNexis (up to three addresses per parent, a maximum of six addresses per family) to send e-vites to these events, with RSVP capabilities provided through Eventbrite.

The study team sent 1,809 invitations to unique email addresses, of which 415 emails were found to be undeliverable or incorrect; 1,394 were successfully delivered. While 258 recipients clicked the link to the Eventbrite page, no confirmed responses were received for the events. One case family contacted the study team through the publicly available study email address to posit a question about the events, but no families expressed interest in attending the information sessions or completing the online survey. The lack of interest in attending these events was most likely due to remaining COVID school closures and protocols.

Control families were sent an initial mailing between May-September 2022. The study team was permitted to pivot to electronic methods of contact for the second mailing, and emails were sent September 8-22. Priority was given to contacting matched controls of the cases who had already completed an interview. Once a control for each case and each group had participated, and the survey was deemed eligible (completing the residential history at a minimum), no more controls for that case were contacted. Only a few matched controls were contacted at a time to reduce the number of duplicate controls, and to minimize extraneous recruitment outreach efforts.

Control enrollment was closed on September 27, 2022, to allow the study team sufficient time to clean, analyze, and summarize the data. 8,355 initial recruitment letters were mailed to control families between May-September 2022 and 48,298 reminder letters were sent as emails. Telephone interviewers were given case records of anyone who had not responded to previous mail invitations. These individuals were contacted a maximum of five times in seven days. See **Appendix B** for a summary of activities for recruitment of controls.

Incentives

Incentives were provided for all participants who did not refuse payment. The study team used two University of Pittsburgh-approved incentive programs. Initially, the Vincent Card program was used, which involved sending a payment card loaded with a specified amount of money to the participant after the survey. The participant then called the university, reaching a member of the study team who would activate their card. Participants were followed-up if they did not call to activate their card. A new program, called the Tango Card System, was implemented halfway through the recruitment process to simplify the process and to be more conducive to the new online method of completing the survey independently.

The Tango Card system involved the participants entering an email address at the end of the survey. Upon the survey's completion in the Qualtrics software platform, a link was automatically sent to their provided email address, giving the participants access to a site where a variety of gift cards could be selected. Email addresses could not be used multiple times to receive additional payments. Cases were provided $25 compensation, and controls were provided $15. The decrease in incentive for controls was due to the shortening of the survey, which preceded control participation. Case participants who took the shorter survey had their incentives kept at $25 to align with initial communications about the study. 804 participants completed the study, with 731 accepting and receiving paid incentives.

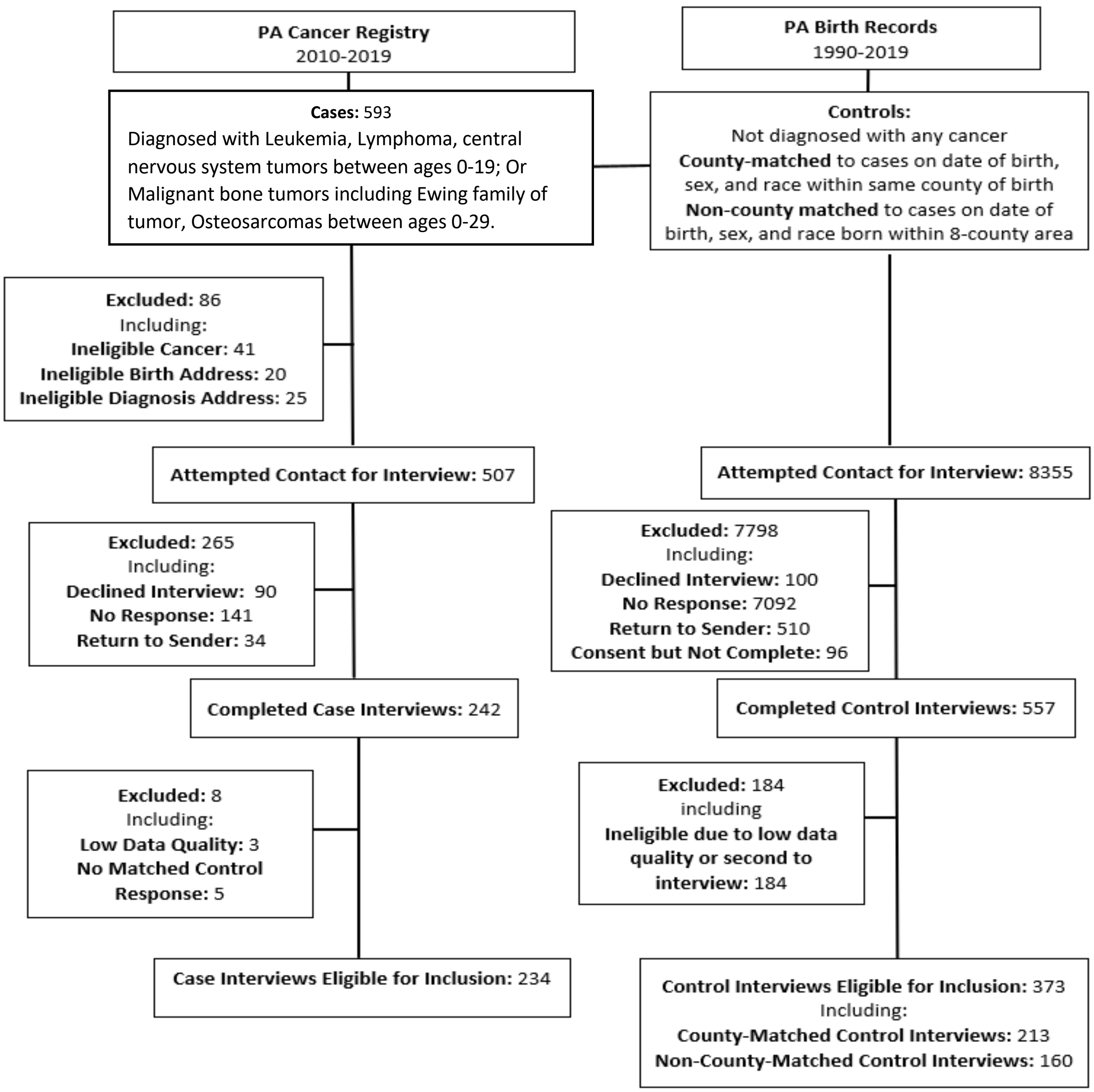
Final Enrollment Numbers

A total of 593 cancer cases were originally identified by the study team. A shift to the use of the ICD-O-3/IARC 2017 coding from an earlier version was recommended by PADOH, leading the study team to reclassify 41 eligible cases to ineligible. Of the 507 remaining eligible cases which the study team attempted to contact, 265 were excluded because 90 refused to participate,141 did not respond to contact attempts, and 34 mailings were "return to sender." An additional 8 cases were excluded from post-data collection; 5 cases were unmatched to a control, and 3 cases were excluded due to low data quality. These exclusions resulted in 234 eligible case interviews.

The research team attempted to contact 8,355 controls, with a priority for interviews with controls whose matched case had already been interviewed. Multiple potential controls for each case were contacted, with the first control who had an eligible response used as the match. 7,798 controls were excluded during recruitment: 7,092 did not respond, 510 were unable to be traced after the letter returned as return to sender, 100 declined interviews, and 96 consented to participate but did not complete the survey. 557 controls were interviewed, but 184 either had low quality data or were second responses for cases who already had a matched control interview completed for that group (county-matched or non-county-matched). 373 controls were included in the analysis. See **Figure 6** for the final enrollment diagram of the case-control study.

Of the 234 eligible case interviews, 147 cases had both county-match and non-county-match controls. A total of 13 cases only had a non-county-matched control and 66 cases only had a county-matched control. After excluding those who refused and the study team was unable to contact, the cooperation rate was 63%.

Figure 6. Enrollment Diagram: Childhood Cancer Case-Control Study



Exposure Measures

UNGD Activity Overview

The primary exposure measure for this study was an inverse distance-weighted index of UNGD activity within 5 miles of parent and child residence. The study team also considered additional buffers: 0.5, 1, and 2 miles. There were four phases of UNGD, including well pad preparation, drilling, hydraulic fracturing, and production, which varied in duration and exposures to potential carcinogens. Therefore, the UNGD activity metric was calculated separately for each of the four phases, for each study subject. Additionally, the study team created an overall activity metric structured the same way as the phase specific metrics, but the duration of activity spanned from the start date of well pad construction until the end of the production phase for each relevant well. Due to the way the phase metrics were structured, the overall activity metric was also equivalent to the sum of the 4-phase metrics. Lastly, the study team calculated well count and inverse distance weighting (IDW) well count to measure the density of and proximity to well sites without integrating duration of exposure. These two metrics were used to align with previous studies.

For wells located in Pennsylvania, data required to calculate the UNGD activity metric were obtained from the Pennsylvania Department of Environmental Protection and the Pennsylvania Department of Conservation and Natural Resources. For wells in Ohio and West Virginia, data were obtained from the Ohio Department of Natural Resources and the West Virginia Department of Environmental Protection, respectively. Due to the difference in the reported data in Ohio and West Virginia (provided annually, rather than daily), the study team was unable to incorporate these data into analyses. Although the analyses focus on residences within the bounds of the eight-county study, the study team had to account for residences located on the geopolitical borders of the study region. To account for this, buffer regions that extended five miles into adjacent counties were included and exposure data within these buffer regions were captured. UNGD phase descriptions are below:

1. **Well pad preparation** – the process of preparing a site where one or more wells were located. It is defined as the period beginning 30 days before the first well on the pad is spudded and ending when the first well is spudded.
2. **Drilling** – the creation of the wellbore. This phase begins on the well's spud date and ends on the drilling completion date; the median for the wells was 104 days.
3. **Hydraulic fracturing** – the process of injecting large volumes of water at high pressure into the wellbore to fracture the shale layer. This period is defined as beginning on the stimulation commencement date and ending on the stimulation completion date. Hydraulic fracturing may be repeated over time for a given well. The median for the wells was 12 days.
4. **Production** – the process of collecting natural gas or oil that—following hydraulic fracturing—travels through the wellbore to the surface. Production durations are variable. A well was defined as being in production for reporting periods when production was indicated and reported production volume was non-zero. The minimum amount of time in the production phase was 30 days (as per how the data were reported). The maximum number of days was 8,769 days. The mean number of days was 2,239 and the median was 2,193 days. An individual well could have had multiple production periods with gaps in which the well was inactive. Calculations include all production period durations but not the gaps between them.

UNGD Exposure Metrics Calculation

Inverse distance weighting (IDW) is a metric used to account for both the proximity and density of wells within a designated buffer distance from a participant's residence. It is a commonly used metric in environmental epidemiological studies. The metric includes a numerator value which is typically 1 but can also take on other quantifying values, such as daily volume of gas production or well depth, adding further information to the metric. The denominator is a measure of distance, typically the distance measured squared. Then these individual fractions are summed across all wells located within a designated buffer distance. See **Figure 7**.

In previous studies, a well was included in the IDW metric if it was both within the designated buffer and there was at least one day of overlap between the well's activity and the participant's study period of interest. This kind of metric did not account for the duration of overlap. For example, two wells that were equidistant from a participant's residence would have made the same contribution to their exposure metric, even if one well was active for one day, whereas the other for one year during the participant's study period. The study team created this metric because it was commonly used in existing literature. To account for duration of exposure, the study team also created an overall activity metric that integrated both the distance and duration of every active well.

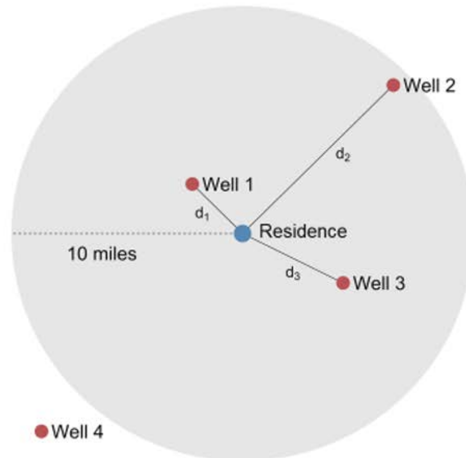
To include a duration element, the numerator for the IDW overall activity metric, as well as the well pad construction, drilling metrics were the sum of days of activity overlap, over the distance squared of each well. This number was summed across all wells within the designated buffer distance. The numerator for IDW hydraulic fracturing and production metrics was well depth in meters and daily average volume of gas production in cubic meters (m^3), respectively, summed over the days of overlap between each respective phase and the participant's study period, then summed across all wells within the designated buffer distance. These two metrics were calculated with additional information to examine how well depth and gas production volume contributed to exposure metric for a given participant.

An IDW overall activity metric and well count metric was calculated as the primary exposure variables. Additionally, 4 IDW metrics corresponding to each phase were calculated as secondary exposure variables. An additional metric of well count (without the use of IDW) was calculated. While examining each phase alone may introduce some issues because many individuals can be exposed to more than one phase simultaneously, the analysis can still contribute to the study's overall conclusions. These 7 metrics were calculated for each residence of the case or control subject. Because each participant could move multiple times during the period of exposure, these metrics were first calculated by residence and then aggregated to create one metric per participant. Further description about how metrics were aggregated provided in the Data Processing section.

Figure 7. Inverse Distance Weighting Example

Inverse distance weighting is a method for calculating exposure to nearby locations of interest, such as UNGD wells.

- The resulting IDW metric not only takes into account the number of wells nearby a residence, but also how close the wells are.
- Wells located close to the residence (like Well #1) contribute more to the IDW metric value, while wells farther away (like Well #2) contribute less.
- Often a buffer distance is used as a boundary, beyond which a well (like Well #4) no longer contributes to the IDW metric value.



Definition of Time Periods

A participant's study period of interest included two time periods. Pregnancy (exposure time window 1, or T1) was defined as conception through date of birth. Date of conception was calculated by subtracting gestational age (in weeks) from the date of birth. Total exposure (exposure time window 2, or T2) was defined as date of birth through the index date, which was date of cancer diagnosis for cases. The same date was applied to controls so the period for both cases and controls was identical.

UNGD activities for a given well had 4 phases as described previously. The duration of each phase was defined in **Table 4**. Each of the data was found, or calculated, using datasets from the Pennsylvania Department of Environmental Protection and the Pennsylvania Department of Conservation and Natural Resources. If a phase for well or well pad overlapped with the case's study exposure time windows T1 and/or T2, all or in part, the overlapping portion of that phase contributed to the calculation of the activity metric for that individual case. See **Tables 5a** and **5b** for the equations of these metrics with an explanation of each term.

Table 4. Definition of UNGD Activity Metric Phase Durations

Metric	Variable name	Definition of Duration
1	Overall Activity	Production period end date minus start date of the well pad preparation variable minus (if applicable) periods of inactivity between production periods
2	IDW Well Count	Numerator was 1 if there were any days overlap between spud date until the most recent production period end date (wells can have multiple production periods), and the participant's exposure period
3	Well Count	Count of 1 if there were any days overlap between spud date until the most recent production period end date (wells can have multiple production periods over time), and the participant's exposure period
4	Well Pad Preparation	Spud date minus 30 days
5	Drilling	Stimulation commencement date minus spud date +1 day
6	Hydraulic Fracturing	Stimulation completion date minus the commencement date + 1 day
7	Production	Production period end date minus production period start date
*Spud date is a fracking industry term meaning the first day of drilling.		

Table 5a. Definition of Primary UNGD Activity Metrics

Metric	Variable Name	Calculation of phase-specific activity metric
1	Overall Activity	$\text{Overall well activity for maternal residence j} = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{I_A(K)}{d_{ij}^2}$ Where: • *n* was the number of wells within 0.5, 1, 2, or 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of conception and *l* the date of birth (for T1)*,* or *k was* equal to date of birth and *l* the index date (for T2) • $I_A(K)$ was equal to 1 when $d_{ij} \le 0.5$, 1, 2, or 5 miles, respectively, and the overall activity (from well pad construction to the end of production not including any inactive periods of production for a given well) overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise • d^2_{ij} was the squared distance (m^2) between well *i* and maternal residence *j*
2	Well Count IDW	$\text{IDW well count for maternal residence j} = \sum_{i=1}^{n}\frac{I_A(K)}{d_{ij}^2}$ Where: • *n* was the number of wells within 0.5, 1, 2, or 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of gestation and *l* the date of birth*,* or *k* was equal to date of birth and *l* the index date for maternal residence *j* • $I_A(K)$ was equal to 1 when $d_{ij} \le 0.5$, 1, 2, or 5 miles, respectively, and the activity of a well (between spud date and the end date of the last production period) overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise • d^2_{ij} was the squared distance (m^2) between well *i* and maternal residence *j*
3	Well Count* *(Results for this metric presented in **Supplement**)	$\text{Well count metric for maternal residence j} = \sum_{i=1}^{n}\sum_{k=1}^{l} I_A(K)$ Where: • *n* was the number of wells within 0.5, 1, 2, or 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of gestation and *l* the date of birth*,* or *k* was equal to date of birth and *l* the index date for maternal residence *j* • $I_A(K)$ was equal to 1 when $d_{ij} \le 0.5$, 1, 2, or 5 miles, respectively, and the activity of a well (between spud date and the last production period end date) overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise

Table 5b. Definition of secondary phase specific UNGD activity metrics

Phase	Phase name	Calculation of phase-specific activity metric
4	Well pad preparation	$$\text{Phase 1 metric for maternal residence j} = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{I_A(K)}{d_{ij}^2}$$ Where: • *n* was the number of well pads within 0.5, 1, 2, or 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of gestation and *l* the date of birth (T1), or *k* was equal to date of birth and *l* the index date (T2) • $I_A(K)$ was equal to 1 when $d_{ij} \leq$ 0.5, 1, 2 or 5 miles, respectively, and the phase overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise • d^2_{ij} was the squared distance (m^2) between well pad *i* and maternal residence *j*
5	Drilling	$$\text{Phase 2 metric for maternal residence j} = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{I_A(K)}{d_{ij}^2}$$ Where: • *n* was the number of wells within 0.5, 1, 2, 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of gestation and *l* the date of birth (T1), or *k* was equal to date of birth and *l* the index date (T2) • $I_A(K)$ was equal to 1 when $d_{ij} \leq$ 0.5, 1, 2, or 5 miles, respectively, and the phase overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise • d^2_{ij} was the squared distance (m^2) between well *i* and maternal residence *j*
6	Hydraulic fracturing	$$\text{Phase 3 metric for maternal residence j} = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{w_i \times I_A(K)}{d_{ij}^2}$$ Where: • *n* was the number of wells within 0.5, 1, 2, or 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of gestation and *l* the date of birth (T1), or *k* was equal to date of birth and *l* the index date (T2) • w_i was the depth in meters of well *i* • $I_A(K)$ was equal to 1 when $d_{ij} \leq$ 0.5, 1, 2, or 5 miles, respectively, and the phase overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise • d^2_{ij} was the squared distance (m^2) between well *i* and maternal residence *j*
7	Production	$$\text{Phase 4 metric for maternal residence j} = \sum_{i=1}^{n}\sum_{k=1}^{l}\frac{v_i \times I_A(K)}{d_{ij}^2}$$ Where: • *n* was the number of wells within 0.5, 1, 2, or 5 miles of maternal residence *j* • *k* was equal to the date of the beginning of gestation and *l* the date of birth (T1), or *k* was equal to date of birth and *l* the index date (T2) • v_i was the daily average produced gas volume (m^3) of well *i* , which was calculated as the reported produced gas volume during the reporting period divided by the number of days the well was actively producing during that reporting period. • $I_A(K)$ was equal to 1 when $d_{ij} \leq$ 0.5, 1, 2, or 5 miles, respectively, and the phase overlapped with the defined exposure time window (T1 or T2), or equal to 0 otherwise • d^2_{ij} was the squared distance (m^2) between well *i* and maternal residence *j*

Calculating IDW Metrics

Addresses were geocoded using ArcMap 10.6 to calculate distances between the wells and residences. Distances were calculated between every residence and well within the study area in MySQL server. Once distances were calculated, data was filtered to include only those that were closer than, or equal to, each respective buffer distance 0.5, 1, 2, and 5 miles. Unexposed individuals were those who had never lived within 5 miles of any UNGD site. Time spent in each residence was truncated for each person to ensure that the dates were within the study periods of interest for each person (T1 – conception to birth, and T2 – birth to the diagnosis/index date). Subsequently, the days that overlapped between time spent in each residence and well activity was calculated. For the hydraulic fracturing and production metrics, the days of overlap were multiplied by well depth and average daily gas volume production, respectively. IDW metrics were built by dividing these numerators by the distance in meters squared for all wells located within each residence's buffer distance. These numbers were then aggregated across all wells for one metric per residence. For those who did not remain consistently within the study area, the study team developed methods to handle lapses in exposure estimation. To aggregate exposure metrics across residences for each case and control, a dataset representing individual participants was used. See **Appendix B** for in-depth descriptions of the geocoding process and methods used to handle incomplete data, as well as calculation methods.

Other UNGD-Related Exposures

Impoundment Ponds

Impoundment ponds store water and other fluids from the hydraulic fracturing process. Using SkyTruth, a nonprofit that uses satellite imagery to identify the locations of possible environmental exposure sites, locations and proximity measures were located and created using the same process described above.

Compressor Stations

Compressor stations are facilities where natural gas is received, repressurized, and sent back out in pipelines. Compressor station data was obtained from the PADEP. Their database was used to identify locations of compressor stations and create inverse distance-weighted proximity measures described above.

Waste Facilities

Waste facilities store waste from the hydraulic fracturing process. Waste facility data was obtained from the PADEP. Their database was used to identify locations of waste facilities and create inverse distance-weighted proximity measures described above.

Other Environmental Exposures

In addition to the UNGD activity metrics, the study team also considered additional sources of environmental exposures in the study area during the study period. These included additional components of oil and gas-related activity (e.g., impoundment ponds, compressor stations, waste disposal facilities), other industrial activities (e.g., toxic release inventory sites), and water source measures. Inverse distance-weighting and other modeling approaches were used, as appropriate, to quantify exposure to these additional sources using the same defined buffer zones.

The study team utilized the following environmental exposures including Uranium Mill Tailing Remedial Action (UMTRA) sites, Toxic Release Inventory (TRI) sites, and Superfund sites. The exposure variables created for UMTRA, TRI, Superfund sites were IDW metrics where the numerator was 1 and denominator was the distance in meters squared summed across each respective site. There was no duration component included. The same buffer distances for UNGD activity metrics were considered. The water source variable was a dichotomous variable with public or private source of water. Below are detailed descriptions of these environmental exposures.

UMTRA Sites

There were four UMTRA sites in the study area. Mill tailings are defined as the sandy waste material from a conventional uranium mill. Milling is the first step in making fuel for nuclear reactors from natural uranium ore. UMTRA sites are areas designated by the US Department of Energy who monitor the clean-up of these mills and prevent further contamination of ground water. The IDW was calculated for the four sites in the study area, as well as the eleven sites outside of Pennsylvania, in case the participants' residential history included areas near those sites.

TRI Sites

Facilities in the United States must report toxic chemical releases to the EPA through the TRI program. For the present analysis, the study team downloaded the 2015 data on all TRI inventory sites for the eight-county study area and all surrounding counties. The year 2015 was chosen as a representative time-point based on the midpoint of the diagnosis time (i.e., 2010 -2019) of cancer cases included in the study. For more information on TRI, visit https://www.epa.gov/toxics-release-inventory-tri-program.

Superfund Sites

Superfund is an environmental remediation program established by the EPA. The program is designed to investigate, and clean-up sites contaminated with hazardous substances and include seven EPA PA sites within the eight-country area, and several sites within the study area.

Other Covariates

In the present analysis, in addition to matching factors on age, sex, race, and county of residence between cases and controls, the following set of variables were considered as potential confounders derived from birth records. These covariates are included in all of the logistic regression models.

1. Maternal age at childbirth
2. Maternal education level (a measure of socioeconomical status)
3. Maternal smoking status (any time during pregnancy) reported at childbirth
4. Gestational age in weeks at birth
5. Birth weight of the study subject

Definition of Exposed and Unexposed

IDW metrics are commonly summarized into levels of exposure for increased ability to meaningfully interpret results. Means and standard deviations (SDs), and medians and inter-quartile values were calculated for each of 7 UNGD activities metric for T1 and T2 time periods for all buffer distances. The distributions of all UNGD activity metrics were used to determine dichotomous exposure or exposure by tertiles or quartiles. Cut points in these variables (between exposed and unexposed or between levels of exposure) are set specifically to increase the contrast.

Few participants in any one level of exposure may yield unstable risk estimates with wide 95% CIs. Beyond this practice, there is currently no agreement in the literature on the best way to summarize IDW variables. The study team chose to display results for several distinct kinds of summary variables where appropriate to see how results may have shifted between options. Four different summary variables were provided for all IDW metrics when there were appropriate numbers of participants within exposure levels as described below:

1. **Dichotomous Exposure** – This variable takes on values of either an exposed or unexposed category. The exposed category was defined for individuals who had any history of residence that was located within 5 miles of any UNGD activity, whereas unexposed category was those who did not have a history of residence within 5 miles of UNGD activity. The unexposed group was used for all analyses for different UNGD-derived metrics described below.
2. **Exposure levels within 5-mile or 2-mile buffer zone** – Exposed individuals were further divided by level of cumulative exposure to UNGD activities over time within the defined buffer zone. The median value among the control group was used to classify individuals into high or low category— tertiles classified individuals into the lowest, middle, and highest-thirds of exposure, and the quartiles classified individuals into the lowest, middle-low, middle-high, and highest-quarters of exposure. In the risk modeling, the unexposed group (defined above) was always used as the reference group.
3. **Proximity measure of UNGD activity** – The proximity measure (i.e., buffer zone) was defined as the shortest distance from a residence to any UNGD activity. Conventional cut-off values [0-0.5], (0.5-1], (1-2] and (2-5] miles were used when appropriate. The reference group consisted of individuals who did not have any wells within 5 miles as defined above. When there were too few subjects in each category, the cut points were set as [0-2], and (2-5]. A square bracket indicates that the value was included within the bound, whereas a parenthesis indicates the value was not included within the bound.
4. **Standardized exposure using phase specific z-score values** – IDW metrics for each phase (well pad construction, drilling, hydraulic fracturing, and production) were calculated and standardized by the standard deviation (i.e. the z-score). The phase-specific z-scores were summed using the following formula: $\sum_{ij}^{k} \frac{x_{ij}-\mu_{.j}}{\sigma_{.j}}$, where i is for subject; j, specific phases of UNGD activities (k=4); x, individual measurement of phase-specific UNGD activity; μ, mean; and σ, standard deviation. The summed z-score was another measure of total UNGD activities per individual exposure. The z-score was unitless and accounted for different values and units of all phase-specific UNGD activities.

Statistical Analysis

Primary Strategy

Descriptive statistics were computed and assessed for all outcome and exposure measures, covariates, and characteristics of the study participants. For continuous variables, mean/standard deviation and median/inter quartile range were used; for categorical variables, frequency/percentiles were used. These variables were estimated for the total population and for the birth record-based and survey-based populations separately and stratified by case-control status and various covariates. Chi-square testing was used to compare differences in percentages for social/demographic and maternal characteristics between groups (e.g., cases vs. controls) when categorical; t-tests were used to evaluate differences in means between groups when continuous. When appropriate, nonparametric tests were used.

The study's main aim was to examine the link between UNGD activity and childhood cancer. As such, logistic regression modeling was used to assess this relationship. To preserve the matched study design, conditional logistic regression modeling was done whenever possible. However, some analyses were performed using an unconditional model including the matching variables as covariates.

Separate conditional logistic regression models were used to estimate ORs and the 95% CIs for all four types of cancer combined (i.e., leukemia, lymphoma, CNS tumors, and bone cancer) comparing exposed with unexposed, as well as comparing various levels of exposure by buffer zone and/or levels of overall UNGD activity. The regression analyses were performed, with and without adjustment for additional covariates. In addition to the primary exposure (UNGD metrics) variable, the multivariable-adjusted models included the following covariates: maternal age at childbirth (continuous), maternal education level (≤ 8^{th} grade, high school, some college, or college degree or higher), maternal smoking status at childbirth (yes/no), gestational age (continuous in weeks), birthweight (continuous in grams), TRI (delineated as non-exposed or exposed within 5 miles), UMTRA (non-exposed or exposed within 5 miles), as well as for Superfund sites (non-exposed or exposed within 5 miles).

Significance testing was performed for individual ORs, as well for evaluation of linear trend for increasing level of UNGD activities using an ordinal variable (i.e., 0 for non-exposed and 1, 2 and 3 for tertiles or 1, 2, 3, 4 for quartiles) with the risk of disease of interest. Similar logistic models were used for the decreasing buffer zone (non-exposed, 2-5 miles, 1-2 miles, 0.5-1.0 miles, and 0-0.5 miles) with the risk of disease of interest. All ORs in this report are shown with 95% CIs for UNGD activities and other exposure variables with adjustment for additional covariates. These models were used to analyze data for all three study populations (two survey-based and one birth record-based).

Although underpowered, regression modeling was done for each of the four individual cancer types. The study team believed it was important to separately examine them due to their different biological characteristics. For EFOT (n=20), unconditional logistic regression modeling was performed separately from other malignant bone tumor cases by including all controls in both survey- and birth record-based studies with adjustment for matching variables (i.e., age at diagnosis, sex, race/ethnicity, and county of residence).

Primary Study Population: Use of the Birth Record Study

The primary study population for analysis was the 498 cancer cases and their county-matched controls. Information on the mothers' and newborns' residence and characteristics from birth certificates was extracted from both cancer registry and birth certificates. For analyses of all malignancies combined, this samples (i.e., 498 cases and 498 matched controls) has sufficient statistical power (>80%) to detect odds ratio of 1.5 and greater assuming 25% UNGD exposure within the control group; when exposure among controls is 20%, there is high power (>90%) to detect odds ratios of 1.75 and greater. Furthermore, this sample had sufficient power to detect odds ratios of 1.75 and greater when exposure among controls is 10%. **(Table 6A).** For analyses of site-specific cancers, power is shown in **Table 6B-D** can detect odds ratios of 2.0 for leukemia and CNS and 2.25 for lymphoma with 80% power within the exposure ranges shown. Power estimates assume a two-sided test with alpha = 0.05, a value of 0.20 for the correlation of exposure status in the matches. Power estimates were calculated using https://sampsize.sourceforge.net/iface/s3.html#ccp).

Table 6: Estimated Power to Detect a Specified Odds Ratio and Probability of Exposure in the Control Sample: (Based on Sample Size Available for Study)

6A. 498 case control pairs

	Odds Ratio				
Probability of exposure in controls	1.5	1.75	2.0	2.25	2.5
0.05	0.326	0.582	0.796	0.922	0.977
0.10	0.543	0.841	0.966	0.996	1.0
0.15	0.684	0.935	0.993	1.0	1.0
0.20	0.772	0.970	0.998	1.0	1.0
0.25	0.826	0.983	0.999	1.0	1.0

6B. Leukemia 157 case control pairs for the Birth Record Study of 498 Cancer Cases

	Odds Ratio				
Probability of exposure in controls	1.5	1.75	2.0	2.25	2.5
0.05	0.129	0.219	0.327	0.447	0.567
0.10	0.207	0.37	0.546	0.705	0.827
0.15	0.272	0.483	0.683	0.832	0.922
0.20	0.323	0.564	0.765	0.893	0.958
0.25	0.363	0.619	0.814	0.924	0.974

6C. Lymphoma 105 case control pairs for Birth Record Study of 498 Cancer Cases

	Odds Ratio				
Probability of exposure in controls	1.5	1.75	2.0	2.25	2.5
0.05	0.0988	0.157	0.228	0.31	0.398
0.10	0.151	0.2599	0.388	0.521	0.646
0.15	0.195	0.342	0.504	0.655	0.778
0.20	0.2299	0.405	0.584	0.736	0.846
0.25	0.2578	0.451	0.637	0.784	0.883

6D. CNS 193 case control pairs for the Birth Record Study of 498 Cancer Cases

	Odds Ratio				
Probability of exposure in controls	1.5	1.75	2.0	2.25	2.5
0.05	0.15	0.261	0.394	0.533	0.664
0.10	0.246	0.441	0.639	0.796	0.899
0.15	0.324	0.569	0.774	0.903	0.965
0.20	0.386	0.655	0.848	0.946	0.984
0.25	0.433	0.712	0.888	0.966	0.991

In contrast and as shown in **Table 6E**, the resulting sample size of the survey 213 cases and 213 matched controls would not provide sufficient power to consider individual cancer specific sites (e.g. leukemia). For all sites combined, however, the resultant sample size *is powered* to detect an odds ratio 2.00 or greater with 80% power. Power estimates assume a two-sided test with alpha = 0.05, a value of 0.20 for the correlation of exposure status in the matches. Please see **Supplementary Tables S3-5** for the overall four malignancies combined risk estimates involving the survey-based population and a few descriptive tables for this second arm of the study.

6E. 213 case control pairs with two-sided test (Survey Sample size) Overall Combined Cancer Risk

	Odds Ratio				
Probability of exposure in controls	1.5	1.75	2.0	2.25	2.5
0.05	0.162	0.285	0.439	0.577	0.71
0.10	0.267	0.479	0.684	0.836	0.927
0.15	0.353	0.612	0.815	0.929	0.98
0.20	0.419	0.699	0.882	0.964	0.991
0.25	0.469	0.755	0.917	0.978	0.996

The decision to use birth residence as the primary location for determining UNGD activity until diagnosis comes into question if the case or control moves during the time from birth until diagnosis. This can lead to misclassification of the exposure and can affect exposure estimates. We carried out a cross tabulation of the county of birth residence for the 498 cases using birth records and the residence county at time of diagnosis using PA Cancer registry. Shown in **Table 7A,** there is high agreement within this study population in that over 85% of cases' parents remained in SW PA counties and the majority also remained within the same county over this period. Likewise shown in **Table 7B** are the results for the controls interviewed for their residential history as part of the survey study. Similarly, the cross tabulation indicates that there is high concordance of residence of controls remaining in the same county of their child's birth and maternal residence.

Table 7A. County of the mother's residence when giving birth, vs. County at diagnosis for the 498 childhood cancer cases

Child's Birth County	Child's Diagnosis County								
	Allegheny*	Armstrong	Beaver	Butler	Fayette	Greene	Washington	Westmoreland	Total	%
Allegheny-**outPGH	188	0	1	8	1	0	6	9	213	88.3
Armstrong	0	13	0	0	0	0	0	3	16	81.3
Beaver	1	1	30	3	0	0	0	0	37	81.1
Butler	0	0	1	55	0	0	0	0	58	94.8
Fayette	2	0	0	0	23	1	2	1	29	79.3
Greene	0	0	0	0	0	9	3	0	12	75.0
Washington	4	0	0	0	0	2	49	0	55	89.1
Westmoreland	7	0	0	0	1	0	1	78	87	89.7
Total	204	14	32	68	25	12	61	91	507	

Table 7B. County of the mother's residence when giving birth vs county at diagnosis for 213 controls

Child's Birth County	Child's Diagnosis County								
	Allegheny	Armstrong	Beaver	Butler	Fayette	Greene	Washington	Westmoreland	Total	%
Allegheny	92	0	1	1	0	0	4	1	99	92.9
Armstrong	0	4	0	0	0	0	0	0	4	100
Beaver	2	0	14	2	0	0	0	0	18	77.8
Butler	2	0	0	16	0	0	0	0	18	88.9
Fayette	0	0	0	0	6	0	0	1	7	85.7
Greene	0	0	0	0	0	6	1	0	7	85.7
Washington	1	0	0	1	0	0	24	0	26	92.3
Westmoreland	0	1	0	0	0	0	0	39	40	97.5
Total	97	5	15	20	6	6	29	41	219*	

*Six controls were excluded due to low data quality or did not meet the resident location requirements

III. Results

Birth Record Sample Characteristics

Table 8 presents the distribution of the 507 childhood cancer cases by primary site for the Birth Record Study. These are newly diagnosed cases excluding relapses and secondary diagnoses. CNS and miscellaneous intracranial and intraspinal neoplasms comprised the largest group, with 38.3% of all cases, followed by leukemias and myeloproliferative diseases accounting for 32.5%, lymphomas (20.7%), and malignant bone tumors including EFOT (8.5%). (See **Supplementary Table S1** for more details).

Table 9 presents the number of total childhood cancer cases for the birth record study by county, year of birth, age group and year of diagnosis (2010-2019). Among the 507 childhood cancer cases eligible for the study, Allegheny County, being the most populous, contributed 204 (40.2%) of these cases followed by Westmoreland, Washington, and Butler counties with 90, 68, and 61 cases, respectively. Fewer cases were included in the 1990-1994 birth cohort as some of children "aged out", (i.e., older than 19 years for the period of cancer diagnosis from 2010-2019). The number of cases by year at diagnosis appears to be evenly distributed from 2010 to 2019. The distribution for the four childhood cancers for ages 0 to 19 years was similar within the total study population, as well as for the two survey populations. They were also similar to the national data recorded by the NCI SEER Program (Cronin et al, 2022).

Table 8 Primary Classes of Childhood Cancer Included in the Birth Record Study (2010-2019)

Primary Cancer Classes	**All Cases N (%)**
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	165 (32.5)
II. Lymphomas and reticuloendothelial neoplasms	105 (20.7)
III. CNS and miscellaneous intracranial and intraspinal neoplasms	194 (38.3)
IV. Malignant bone tumors including EFOT	43 (8.5)†
TOTAL	507 (100)

† Including 20 cases of Ewing tumor and related sarcomas of bone.

Table 9. Characteristics of Childhood Cancer Cases in the Birth Record study, South Western PA 2010-2019

	Total cases (N=507)
	N (%)
Year of Birth	
1990-1994	46 (9.1)
1995-1999	107 (21.1)
2000-2004	115 (22.7)
2005-2009	104 (20.5)
2010-2014	96 (18.9)
2015-2018	39 (7.3)
County of Residence	
Allegheny†	204 (40.2)
Armstrong	14 (2.8)
Beaver	32 (6.3)
Butler	68 (13.4)
Fayette	25 (4.9)
Greene	12 (2.4)
Washington	61 (12.0)
Westmoreland	91 (18.0)
Year of Diagnosis	
2010	60 (11.8)
2011	63 (12.4)
2012	45 (8.9)
2013	52 (10.2)
2014	47 (9.3)
2015	51 (10.1)
2016	52 (10.2)
2017	41 (8.1)
2018	51 (10.1)
2019	45 (8.9)
Age Group at Diagnosis	
0-4	149 (29.4)
5-9	98 (19.3)
10-14	111 (21.9)
15-19	146 (28.8)
20-24‡	2 (0.4)
25-29‡	1 (0.2)

† Excluding the City of Pittsburgh where UNGD is not permitted.
‡ Applicable for malignant bone tumors only.

Table 10. Distributions of Sociodemographic Characteristics of Childhood Cancer Cases Using Birth Record Information in the Birth Record-Based Studies with County-Matched Controls

Sociodemographic Characteristic	Birth Record-Based Study	
	Cases (%)	*Controls (%)*
Total number	498 (100)	498 (100)
Sex at Birth		
Female	216 (43.4)	216 (43.4)
Male	282 (56.6)	282 (56.6)
Maternal Age (years)		
<20	33 (6.6)	25 (5.0)
20-24	79 (15.9)	83 (16.7)
25-29	132 (26.5)	124 (24.9)
30-34	146 (29.3)	160 (32.1)
≥35	108 (21.7)	106 (21.3)
Maternal Race		
White	480 (96.4)	480 (96.4)
Black	12 (2.4)	12 (2.4)
Other	5 (1)	6 (1.2)
Maternal Education [1]		
≤ 8th Grade	2 (0.4)	3 (0.6)
Some High School	36 (7.2)	25 (5)
High School Diploma	145 (29.1)	141 (28.3)
Some College	124 (24.9)	123 (24.7)
College Degree or Higher	186 (37.4)	198 (39.8)
Unknown	5 (1)	8 (1.6)
Number of Prenatal Visits		
0-7	41 (8.2)	48 (9.6)
8-12	241 (48.4)	245 (49.2)
13-16	177 (35.5)	176 (35.3)
≥17	20 (4.0)	17 (3.4)
Unknown	19 (3.8)	12 (2.4)
Birth weight		
≤2500 g	28 (5.4)	23 (4.6)
2501- 4000 g	411 (82.5)	426 (85.5)
>4000 g	60 (12.1)	49 (9.8)
Unknown	28 (5.4)	23 (4.6)
Smoking during pregnancy[2]		
Never	397 (79.7)	408 (81.9)
Ever	92 (18.5)	89 (17.9)
Unknown	9 (1.8)	1 (0.2)
Gestation in weeks		
Mean (±S.D.)	38.7 (1.8)	38.8(1.6)

[1] p value=.08 survey based education >college; p value<.01 for birth record based> college

[2] p value=.28 survey based ever smoked during pregnancy ; p value<.026 for birth record based smoking

Maternal and Birth Characteristics of Birth Record Based Study

Table 10 presents characteristics of cancer cases and their matched controls for the birth-record based study. Childhood cancer cases and their matched controls were 56.6% male, and approximately 96% of the maternal study population reported a race of white. Case mothers reported an educational level of some college (24.9%) or completed college degree or higher (37.4%). The control distribution of education was similar (24.7% and 39.8%, respectively). There was also a similar proportion of cases and county-matched controls with a birth weight between 2501-4000g (82.5% and 85.5%, respectively). The proportion of mothers who reported never smoking during pregnancy was similar for cases and county-matched controls (79.7% and 81.9%, respectively). The birth weight of case infants versus control infants between 2501-4000g was also similar (82.3% and 85.6%, respectively). Similarly, 79.7% of mothers of cases and 82% of mothers of controls reported never having smoked cigarettes during their pregnancy. The average gestational age was 38 weeks for both groups.

Supplementary Table S2 presents the distributions of the eight UNGD activities metrics within a 5-mile radius of the residence among all 498 cancer cases and their 498 county-matched birth certificate controls for the two exposure time windows.

Exposure to UNGD Activity and Risk of Childhood Cancer

The study team analyzed the association between UNGD exposures and risk of four childhood malignancies (lymphoma, leukemia, CNS tumor and malignant bone tumor) combined for all 498 cases and their matched controls based on the information on birth records.

In the birth record-based analyses, the study team presented the results for two exposure time windows separately: T1 was mother's pregnancy period and T2 was from birth to the index date. The index date was the date of malignancy diagnosis for cases and the corresponding date for the matched controls. In addition to matching factors (date of birth, sex, and race), results presented were adjusted for maternal age at childbirth, education level, smoking status at childbirth, as well as gestation age, birthweight, TRI, UMTRA, and superfund site.

Four Malignancy Types Combined

Table 11 presents UNGD activities related to the risk of childhood malignancies. During pregnancy, mothers of 39 (18.3%) cases and of 41 (19.2%) county-matched controls in the survey-based study (213 pairs) reported a history of residence within 5 miles of a UNGD site. In the birth record-based study (498 pairs), the corresponding numbers were 94 (18.9%) cases and 99 (19.9%) controls. Compared with non-exposed group, there was no evidence to support an association between exposure to UNGD activity during mother's pregnancy and risk of malignancy in childhood and adolescence.

In the birth record-based analysis (498 case-control pairs), children diagnosed with any of the four malignancies included in the study were about four times more likely to live in a house within 0.5 miles of a UNGD site than controls (OR=3.94, 95% CI [1.66-9.30], P=0.002). There was a statistically significant linear trend for close-proximity and risk of childhood malignancy (p=0.004) When the subjects were divided into quartiles of overall UNGD activities, increasing levels of these were associated with increased risk of the four childhood malignancies. For example, children diagnosed with any of the four malignancies were more than two times more likely to be in the highest quartile of overall UNGD activities within 2 miles (OR=2.16, 95% CI [1.10-4.25], p=0.026) than their matched controls, and the linear trend for the overall UNGD activities with risk of these malignancies was statistically significant (p for trend=0.032).

Table 11. Overall Unconventional Natural Gas Drilling Activities and Risk of Four Childhood/Adolescent Malignances Combined During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-Based Study with County-Matched Controls (498 case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
T1: During Mother's Pregnancy			
Non-exposed	399	404	1.00
Exposed*	99	94	0.82 (0.47-1.41)
By buffer zone			
Non-exposed	399	404	1.00
(2-5] miles	64	63	0.84 (0.48-1.46)
(1-2] miles	24	22	0.72 (0.31-1.67)
(0.5-1] miles	9	7	0.65 (0.19-2.26)
[0-0.5] miles	2	2	0.81 (0.05-14.62)
P trend‡			*0.3817*
By overall UNGD activities within 5 miles			
Non-exposed	399	404	1.00
Lowest (1st) quartile	24	17	0.63 (0.29-1.34)
Low-middle (2nd) quartile	25	22	0.77 (0.37-1.64)
High-middle (3rd) quartile	25	36	1.40 (0.63-3.14)
Highest (4th) quartile	25	19	0.75 (0.31-1.83)
P trend‡			*0.7587*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

Table 11 Continued. Overall Unconventional Natural Gas Drilling Activities and Risk of Four Childhood/Adolescent Malignances Combined During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (498 case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
T2: From Birth to Index Date§			
Non-exposed	201	187	1.00
Exposed*	297	311	1.24 (0.87-1.78)
By buffer zone			
Non-exposed	201	187	1.00
(2-5] miles	178	170	1.18 (0.82-1.71)
(1-2] miles	72	77	1.49 (0.89-2.51)
(0.5-1] miles	37	38	1.61 (0.85-3.03)
[0-0.5] miles	10	26	**3.94 (1.66-9.39)**
P trend‡			***P=0.0041***
By overall UNGD activities within 5 miles			
Non-exposed	201	187	1.00
Lowest (1st) quartile	74	86	1.40 (0.91-2.14)
Low-middle (2nd) quartile	74	50	0.76 (0.46-1.25)
High-middle (3rd) quartile	74	88	**1.69 (1.01-2.82)**
Highest (4th) quartile	75	87	1.79 (1.00-3.19)
P trend‡			*0.0975*
By overall UNGD activities within 2 miles**			
Non-exposed	201	187	1.00
Lowest (1st) quartile	29	37	1.74 (0.93-3.27)
Low-middle (2nd) quartile	30	32	1.48 (0.77-2.84)
High-middle (3rd) quartile	30	30	1.41 (0.72-2.77)
Highest (4th) quartile	30	42	**2.16 (1.10-4.25)**
P trend‡			***P=0.0321***

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

** The same data for those with UNGD exposure within 2-5 miles of buffer zone were included in this modelling but not presented repeatedly.

Lymphoma

An analysis was carried out on the 105 lymphoma cases and their matched controls using the overall UNGD activity metric with consideration by exposure within five miles versus no exposure within five miles. See **Table 12**. The analysis is shown for both T1 (based on residence during pregnancy till birth) and T2 periods (residency from birth till index date). There is no significant relationship between overall UNGD activity and lymphoma risk for the T1 period. However, for the T2 period involving UNGD activity from birth to date of diagnosis, the point estimate for exposure to UNGD activity was (OR=2.24, 95% CI [0.92-5.47], p=0.076). The data were analyzed by buffer zone, the ORs (95% CIs) of lymphoma for the distance of 2-5, 1-2, 0.5-1, and <0.5 miles from residence to a UNGD site were 2.06 (0.83-5.13), 2.45 (0.77-7.83), 5.05 (1.09-23.39), and 7.71 (1.01-59.00), respectively, compared with non-exposed group (p value for trend=0.015). When the subjects were grouped by the overall UNGD activities over time, the ORs for lymphoma increased with greater levels of UNGD activities within both 5 and 2 miles of buffer zones. For example, the ORs (95% CIs) of lymphoma for children with the first, second, and third tertile of overall UNGD activities limited to two miles of radius surrounding their residences were 2.12 (0.51-8.79), 2.66 (0.66-10.72), and 7.73 (1.63-36.87), respectively, compared with non-exposed individuals (p value for trend=0.020).

When the UNGD activities were summed over the number of standard deviations for each of the four phase-specific UNGD activities, ORs (95% CIs) of lymphoma for children in the first, second, third, and fourth quartile of summed scores were 1.39 (0.44-4.37), 1.89 (0.62-5.80), 4.35 (1.26-15.01), and 5.15 (1.35-19.63), respectively (p values for trend = 0.011), compared with the non-exposed group in the birth record-based analysis.

Table 12. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood Lymphoma During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (105 Lymphoma case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
Period T1: During Mother's Pregnancy			
Non-exposed	89	90	1.00
Exposed*	16	15	0.91 (0.26-3.12)
By buffer zone			
Non-exposed	89	90	1.00
(2-5] miles	10	9	0.96 (0.27-3.48)
(1-2] miles	3	2	0.77 (0.09-6.34)
(0.5-1] miles	1	2	1.82 (0.11-30.83)
[0-0.5] miles	2	2	2.26 (0.06-85.26)
P trend‡			*0.6818*
By overall UNGD activities within 5 miles			
Non-exposed	89	90	1.00
Lowest (1st) quartile	5	1	0.28 (0.03-2.60)
Low-middle (2nd) quartile	5	5	0.82 (0.13-5.06)
High-middle (3rd) quartile	3	6	4.83 (0.4-58.83)
Highest (4th) quartile	3	3	3.59 (0.25-50.69)
P trend‡			*0.4023*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

Table 12. Continued. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood Lymphoma During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (105 Lymphoma case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
Period T2: From Birth to Index Date§			
Non-exposed	40	32	1.00
Exposed*	65	73	2.24 (0.92-5.47)
By buffer zone			
Non-exposed	40	32	1.00
(2-5] miles	39	39	2.06 (0.83-5.13)
(1-2] miles	17	16	2.45 (0.77-7.83)
(0.5-1] miles	6	12	**5.05 (1.09-23.39)**
[0-0.5] miles	3	6	**7.71 (1.01-59.00)**
P trend‡			***0.0149***
By overall UNGD activities within 5 miles			
Non-exposed	40	32	1.00
Lowest (1st) quartile	13	15	1.74 (0.53-5.77)
Low-middle (2nd) quartile	18	11	1.14 (0.35-3.72)
High-middle (3rd) quartile	15	24	**5.68 (1.58-20.48)**
Highest (4th) quartile	19	23	**3.96 (1.01-15.49)**
P trend‡			***0.0155***
By overall UNGD activities within 2 miles**			
Non-exposed	40	32	1.00
Lowest (1st) tertile	8	7	2.12 (0.51-8.79)
Middle (2nd) tertile	10	12	2.66 (0.66-10.72)
Highest (3rd) tertile	8	15	**7.73 (1.63-36.67)**
P trend‡			***0.0201***

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% (CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

** The same data for those with UNGD exposure within 2-5 mile of buffer zone were included in this modelling but not presented repeatedly.

Leukemia

During both the mother's pregnancy and postnatal period, there was no elevated risk of childhood leukemia noted with exposure to any UNGD activities (or overall cumulative activities) or proximity to UNGD sites, in the birth record analysis. In the birth record-based analysis, for the postnatal (T2) period overall, any exposure to UNGD was not associated with the risk of leukemia (OR = 0.79, 95% CI = 0.35-1.79, *P* = 0.574). **See Table 13.**

Table 13. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood Leukemia During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (157 Leukemia case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
Period T1: During Mother's Pregnancy			
Non-exposed	120	122	1.00
Exposed*	37	35	0.73 (0.25-2.10)
By buffer zone			
Non-exposed	120	122	1.00
(2-5] miles	21	25	0.77 (0.27-2.24)
[0-2] miles	16	10	0.27 (0.05-1.36)
P trend‡			*0.1288*
By overall UNGD activities within 5 miles			
Non-exposed	120	122	1.00
Lowest (1st) quartile	8	8	0.89 (0.24-3.27)
Low-middle (2nd) quartile	10	6	0.44 (0.10-1.90)
High-middle (3rd) quartile	9	14	1.12 (0.24-5.25)
Highest (4th) quartile	10	7	0.47 (0.08-2.64)
P trend‡			*0.4337*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.
† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**
‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.
§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.
** The same data for those with UNGD exposure within 2-5 mile of buffer zone were included in this modelling but not presented repeatedly.

Table 13 Continued. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood Leukemia During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (157 Leukemia case-control pairs)**		
	Controls	***Cases***	**OR (95% CI) †**
Period T2: From Birth to Index Date§			
Non-exposed	67	69	1.00
Exposed*	90	88	0.79 (0.35-1.79)
By buffer zone			
Non-exposed	67	69	1.00
(2-5] miles	56	50	0.77 (0.34-1.75)
(1-2] miles	21	20	0.97 (0.28-3.33)
(0.5-1] miles	12	10	0.92 (0.24-3.46)
[0-0.5] miles	1	8	7.69 (0.70-83.91)
P trend‡			*0.3203*
By overall UNGD activities within 5 miles			
Non-exposed	67	69	1.00
Lowest (1st) quartile	25	31	1.16 (0.46-2.90)
Low-middle (2nd) quartile	23	9	0.38 (0.13-1.16)
High-middle (3rd) quartile	26	25	0.98 (0.29-3.27)
Highest (4th) quartile	16	23	1.51 (0.35-6.42)
P trend‡			*0.7676*
By overall UNGD activities within 2 miles**			
Non-exposed	67	69	1.00
Lowest (1st) tertile	14	11	0.62 (0.16-2.4
Middle (2nd) tertile	14	12	0.77 (0.20-2.92)
Highest (3rd) tertile	6	15	3.97 (0.66-23.95)
P trend‡			*0.2648*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

** The same data for those with UNGD exposure within 2-5 mile of buffer zone were included in this modelling but not presented repeatedly.

Central Nervous System (CNS) Tumor

Similarly, analyses for the risk of CNS tumor from exposure to UNGD during the mother's pregnancy and the period from birth to the index date were conducted separately. There was no association between any measure of UNGD exposure and risk of childhood CNS among the 193 pairs of cases and county-matched controls studied. **See Table 14**. In this birth record-based analysis, any exposure to UNGD within five miles of the mother's residence at birth was not associated with the risk of CNS tumor either during pregnancy or from birth to the index date, (OR = 0.85, 85% CI = 0.35-2.03) and OR = 1.28, 95% CI= 0.74-2.22), respectively. There was one occurrence of a significant increase in risk of CNS tumor in the T2 period from birth to the index date in the lowest tertile of exposure by overall UNGD activities within two miles (OR= 2.79, 95% CI:1.08-7.24).

Table 14. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood Central Nervous System Tumor During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (193 CNS case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
Period T1: During Mother's Pregnancy			
Non-exposed	151	152	1.00
Exposed*	42	41	0.85 (0.35-2.03)
By buffer zone			
Non-exposed	151	152	1.00
(2-5] miles	29	28	0.84 (0.34-2.06)
(1-2] miles	7	8	1.07 (0.26-4.46)
[0-1] miles	6	5	0.68 (0.13-3.59)
P trend‡			*0.7712*
By overall UNGD activities within 5 miles			
Non-exposed	151	152	1.00
Lowest (1st) quartile	9	8	0.77 (0.18-3.30)
Low-middle (2nd) quartile	10	10	0.99 (0.28-3.47)
High-middle (3rd) quartile	11	14	1.09 (0.34-3.53)
Highest (4th) quartile	12	9	0.56 (0.15-2.03)
P trend‡			*0.5827*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

** The same data for those with UNGD exposure within 2-5 mile of buffer zone were included in this modelling but not presented repeatedly.

Table 14 continued. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood Central Nervous System Tumor During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (193 CNS case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
***Period T2: From Birth to Index Date*§**			
Non-exposed	83	74	1.00
Exposed*	110	119	1.28 (0.74-2.22)
By buffer zone			
Non-exposed	83	74	1.00
(2-5] miles	62	62	1.23 (0.71-2.16)
(1-2] miles	28	30	1.54 (0.69-3.47)
(0.5-1] miles	15	15	1.38 (0.49-3.89)
[0-0.5] miles	5	8	1.96 (0.53-7.26)
P trend‡			*0.2818*
By overall UNGD activities within 5 miles			
Non-exposed	83	74	1.00
Lowest (1st) quartile	29	34	1.32 (0.69-2.50)
Low-middle (2nd) quartile	24	24	1.06 (0.48-2.33)
High-middle (3rd) quartile	24	30	1.55 (0.71-3.35)
Highest (4th) quartile	33	31	1.15 (0.47-2.79)
P trend‡			*0.6205*
By overall UNGD activities within 2 miles**			
Non-exposed	83	74	1.00
Lowest (1st) tertile	13	24	**2.79 (1.08-7.24)**
Middle (2nd) tertile	14	11	0.84 (0.29-2.49)
Highest (3rd) tertile	21	18	1.06 (0.39-2.87)
P trend‡			*0.9850*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.
† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**
‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.
§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.
** The same data for those with UNGD exposure within 2-5 mile of buffer zone were included in this modelling but not presented repeatedly.

Malignant Bone tumors

In the birth record-based study (43 case-control pairs), 3 mothers in the cases and 4 in the controls reported a similar exposure to UNGD activities. No risk of malignant bone tumor was associated with exposure to UNGD activities during mother's pregnancy. See **Table 15**. However, the small sample size of malignant bone tumors provided limited statistical power.

Table 15. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood/Adolescent Malignant Bone Tumor During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (43 case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**
T1: During Mother's Pregnancy			
Non-exposed	39	40	1.00
Exposed*	4	3	0.22 (0.01-8.58)
T2: From Birth to Index Date§			
Non-exposed	11	12	1.00
Exposed*	32	31	1.01 (0.25-4.15)
By Buffer zone			
(2-5] miles	21	15	1.02 (0.25-4.12)
[0-2] miles	11	16	3.32 (0.42-26.24)
P trend			*0.2550*
By overall UNGD activities within 5 miles			
Lowest (1st) tertile	11	9	1.20 (0.25-5.85)
Middle (2nd) tertile	12	9	0.63 (0.1-4.03)
Highest (3rd) tertile	9	13	3.52 (0.30-40.73)
P trend‡			*0.5410*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

Ewing Family of Tumor

In the birth record-based study, Ewings cases, which numbered only 20 in the present study, were compared using unconditional logistic regression to the total sample of 498 controls. This was done to increase the power to assess the relationship of UNGD activities with adjustment by matching variables, age, race, sex and county of birth as well as the other covariates. There were no significant findings from this analysis. **See Table 16.** Additional analysis did not reveal any dose-response relationships for different buffer zones and overall UNGD activities with risk of EFOT (both p values for trend >0.48). To align with previous studies in UNGD and childhood cancer risk in the literature, similar UNGD exposure metrics were created using well counts and IDW well counts. Overall, the associations between these well count measures and risk of childhood malignancies were like those of the newly created UNGD measurements described above. For example, levels of well counts and IDW well counts were associated with higher ORs for lymphoma, CNS tumor, and malignant bone tumor and EFOT. However, none of the point estimates or linear trend tests were statistically significant.

Table 16. Overall Unconventional Natural Gas Drilling Activities and Risk of Childhood/Adolescent Ewing Family of Tumor During Two Exposure Periods in Southwestern PA 2010-2019

Overall UNGD activities by exposure period	**Birth Record-based Study with County-matched Controls (20 cases *vs.* 498 controls)**		
	Controls	***Cases***	**OR (95% CI)†**
T1: During Mother's Pregnancy			
Non-exposed	399	18	1.00
Exposed*	99	2	0.55 (0.10-2.86)
T2: From Birth to Index Date§			
Non-exposed	201	6	1.00
Exposed*	297	14	1.55 (0.46-5.17)
By Buffer zone			
Non-exposed	201	6	1.00
(2-5] miles	178	9	1.50 (0.43-5.21
[0-2] miles	119	5	1.72 (0.36-8.36)
P trend			*0.4879*
By overall UNGD activities within 5 miles			
Non-exposed	201	6	1.00
Low (below median)	148	8	1.62 (0.46-5.7)
High (above median)	149	6	1.39 (0.32-5.96)
P trend‡			*0.6763*

* Exposed included individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls) (T2); non-exposed otherwise.

† All ORs and their 95% CIs for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and the following variables, including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and Superfund site (no, yes). **Odds ratios and confidence ratios which are bolded are significant at P < .05.**

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

Exposure to Other Environmental Risk Sites and Risk of Childhood Cancer

We examined the association for risk of childhood malignancies with exposures to TRI, UMTRA, and Superfund sites using the case and control mothers' residence for the birth-record study. These analyses were adjusted for age at childbirth, maternal education level, maternal smoking, gestational age, and birth weight. Overall, 86.7% of the children diagnosed with any of the 4 malignancies studied and 84.7% of their matched controls had a birth residence within 5 miles of a TRI site. Compared with non-exposed groups, living close to a TRI site was not associated with an elevated risk of 4 childhood malignancies combined. The malignancy-specific analysis revealed that children with leukemia were no more likely to have lived within 0.5-1 miles of a TRI site, *(***Table 17)**, and no consistent dose-response relationship was observed for proximity and level of exposure to TRI with risk of leukemia (both *Ps* for trend >0.32). No association with elevated risk of other childhood malignancy types including lymphoma, CNS tumor and osteosarcoma was observed for exposure to TRI site. (**Table 17**).

The proportions of children who were exposed to UMTRA and superfund sites within 5 miles of residence from birth to the index date were low. Overall, 8.4-10.6% of children in the study had a history of residence within 5 miles of UMTRA and superfund site. There was no increased risk in children for the four childhood malignancies combined nor for leukemia, lymphoma, and osteosarcoma. However, the risk of childhood CNS Tumors was significantly elevated **OR=2.68 (1.11-6.44) p=.028)** (**Table 18.)**

The proportions of children who were exposed to a Superfund site within five miles of residence from birth to index date was 8.8% for cases and 7.8% for controls. For the overall combined four malignancies, the odds ratio of 1.12 (95% CI: .71-1.76) was not significant. Moreover, leukemia, lymphoma, and osteosarcoma showed no significant results. However, the risk of CNS associated with proximity to a superfund site was OR=2.16 (0.96-4.86), p=.06 after adjustment for all covariates. **(Table 19).**

Table 17. Birth Record Exposure to Inverse-Distanced Weighed (IDW) Toxic Release Inventory (TRI) (US EPA) and Risk of Childhood Malignancies in Western Pennsylvania 2010-2019

Exposure to IDW TRI	**Controls**	**Cases**	**OR (95% CI)†**	***P***	***P* for trend‡**
4 Cancer types combined (498 Pairs)					
Non exposed/[5-10] miles	76	66	1 (reference)	-	.5368
[2-5] miles	194	197	1.23 (.81-1.86)	0.3432	-
[1-2] miles	125	132	1.27 (0.8-2.01)	0.3179	-
[.5-1] miles	72	69	1.15 (0.69-1.92)	0.5845	-
[0-.5] miles	31	34	1.31 (0.71-2.42)	0.3909	-
Leukemia (157 pairs)					
Non exposed/[5-10] miles	20	19	1 (reference)	-	0.3228
[2-5] miles	64	61	1.23 (0.55-2.74)	0.6209	-
[1-2] miles	46	43	1.12 (0.48-2.63)	0.7932	-
[.5-1] miles	17	24	1.86 (0.68-5.05)	0.2252	-
[0-.5] miles	10	10	1.61 (0.47-5.55)	0.4535	-
Lymphoma (105 pairs)					
Non exposed/[5-10] miles	16	15	1 (reference)	-	0.3916
[2-5] miles	38	36	1.14 (0.37-3.44)	0.8226	-
[1-2] miles	30	34	1.45 (0.46-4.51)	0.5237	-
[.5-1] miles	17	10	0.59 (0.14-2.51)	0.4749	-
[0-.5] miles	4	10	3.89 (0.71-21.41)	0.1187	-
CNS tumor (193 pairs)					
Non exposed/[5-10] miles	29	29	1 (reference)	-	0.8641
[2-5] miles	82	78	0.99 (0.52-1.91)	0.9844	-
[1-2] miles	40	44	1.16 (0.54-2.46)	0.7096	-
[.5-1] miles	29	31	1.11 (0.51-2.4)	0.8019	-
[0-.5] miles	13	11	0.92 (0.36-2.34)	0.8564	-
Malignant bone tumor (43 pairs)					
Non exposed/[5-10] miles	11	3	1 (reference)	-	0.7340
[2-5] miles	10	22	10.51 (1.47-75.37)	0.0193	-
[0-2] miles	22	18	2.82 (0.52-15.43)	0.2312	-

† Odds ratios (ORs) were adjusted for maternal age at childbirth, maternal education level, maternal smoking status at childbirth, gestation age, and birthweight.

‡ Linear trend test for the exposure variable in ordinal values (1, 2, 3, 4 for quartile) that also included non-exposed.

Table 18. Birth Record Exposure to Inverse-Distance Weighted (IDW) Uranium Mill Tailings Remedial Action (UMTRA) (US DOE) and Risk of Childhood Malignancies in Western Pennsylvania 2010-2019

Exposure to IDW UMTRA	**Controls**	**Cases**	**OR (95% CI)†**	***P***	***P* for trend‡**
4 Cancer types combined (498 Pairs)					
Non exposed/[5-10] miles	456	445	1 (reference)	-	.1884
[0-5] miles	42	53	1.37 (0.86-2.2)	.1884	-
Leukemia (157 pairs)					
Non exposed/[5-10] miles	140	140	1 (reference)	-	.9098
[0-5] miles	17	17	.95 (.37-2.43)	.9098	-
Lymphoma (105 pairs)					
Non exposed/[5-10] miles	95	97	1 (reference)	-	0.5978
[0-5] miles	10	8	0.75 (0.25-2.2)	0.5978	-
CNS tumor (193 pairs)					
Non exposed/[5-10] miles	184	172	1 (reference)	-	**0.0281**
[0-5] miles	9	21	2.68 (1.11-6.44)	**0.0281**	-
Malignant bone tumor (43 pairs)					
Non exposed/[5-10] miles	37	36	1 (reference)	-	0.6164
[0-5] miles	6	7	1.40 (0.38-5.13)	0.6164	-

† Odds ratios (ORs) were adjusted for maternal age at childbirth, maternal education level, maternal smoking status at childbirth, gestation age, and birthweight.
‡ Linear trend test for the exposure variable in ordinal values (1, 2, 3, 4 for quartile) that also included non-exposed.

Table 19. Birth Record Exposure to Inverse-Distance Weighted (IDW) Superfund Site (US EPA) and Risk of Childhood Malignancies in Western Pennsylvania 2010-2019

Exposure to IDW TRI	**Controls**	**Cases**	**OR (95% CI)†**	***P***	***P* for trend‡**
4 Cancer types combined (498 Pairs)					
Non exposed/[5-10] miles	459	454	1 (reference)	-	0.6403
[0-5] miles	39	44	1.12 (0.71-1.76)	0.6403	-
Leukemia (157 pairs)					
Non exposed/[5-10] miles	139	142	1 (reference)	-	0.2679
[0-5] miles	18	15	0.64 (0.29-1.41)	0.2679	-
Lymphoma (105 pairs)					
Non exposed/[5-10] miles	97	99	1 (reference)	-	0.7097
[0-5] miles	8	6	0.82 (0.28-2.4)	0.7097	-
CNS tumor (193 pairs)					
Non exposed/[5-10] miles	182	172	1 (reference)	-	.0545
[0-5] miles	11	21	2.16 (0.96-4.86)	.0612	-
Malignant Bone Tumor (43 pairs)					
Non exposed/[5-10] miles	41	41	1 (reference)	-	0.0612
[0-5] miles	2	2	0.77 (0.1-6.01)	0.8055	-

† Odds ratios (ORs) were adjusted for maternal age at childbirth, maternal education level, maternal smoking status at childbirth, gestation age, and birthweight.
‡ Linear trend test for the exposure variable in ordinal values (1, 2, 3, 4 for quartile) that also included non-exposed.

IV. Discussion

The present study performed three separate analyses derived from 507 cases with childhood cancer newly identified throughout eight counties within Southwestern Pennsylvania between 2010 – 2019, a period of extensive hydraulic fracturing activity. The primary analyses were focused on 498 case-control pairs based on birth certificate data.

The following criteria were used to summarize results:

1. There are no data to suggest/support an increased risk
   a. No statistically significantly elevated odds ratios
   b. Odds ratios at or near 1
   c. Odds ratios below 1 (with or without statistical significance)
2. There are limited data to suggest/support an increased risk
   a. Statistically significantly elevated odds ratios in a low or moderate tertile
   b. Not statistically significant elevated odds ratios in multiple tertiles
3. There are moderate data to suggest/support an increased risk
   a. Statistically significantly elevated odds ratios in multiple low or moderate tertiles
   b. Statistically significantly elevated odds ratios in a high tertile
4. There are strong data to suggest/support an increased risk
   a. Statistically significantly elevated odds ratios in multiple tertiles
   b. Statistically significantly elevated odds ratios that increase across low, moderate, and high tertiles

Table 20. Summary of Results of Association Between UNGD Activities and Childhood Cancer in Southwestern PA 2010-2019

Analysis	**Exposure**	**Four Malignancy Types Combined**	**Lymphoma**	**Leukemia**	**CNS Tumor**	**Malignant Bone Tumor**	**Ewing Family of Tumor**
Birth-record based study with county matched controls (498 pairs)	**Overall UNGD**	**Moderate evidence**	**Moderate evidence**	None	Limited evidence	None	None

Four Childhood Malignancies Combined

In the birth record-based analyses with county-matched controls, there was limited to moderate evidence in support of an association between overall UNGD exposure and the combined four malignancies studied. See **Table 20**. No evidence was observed that exposure to other UNGD-related sites (i.e., compressor station, impoundment pond, and wastewater facility sites) or to other environmental risk sites (i.e., TRI, UMTRA and superfund site) was associated with the risk.

Childhood Lymphoma

This study provided moderate evidence suggesting an association between UNGD activity and childhood lymphoma. Analyses revealed statistically significant elevated ORs in multiple higher levels of overall UNGD activities. ORs for lymphoma increased as residential distances from UNGD sites decreased. These odds also increased as overall UNGD activities within both five miles and two miles of buffer zone increased. respectively. See **Table 12**. Although these positive associations between UNGD activities and risk of lymphoma were stronger in the birth record-based analysis than the survey-based analysis, size of the risk estimates and their direction and magnitude wee similar among the two analyses.

Childhood Leukemia

There was no evidence in support of an association between exposure to UNGD activities and other environmental factors with the risk of childhood leukemia was found in this study. See **Table 13**.

Childhood CNS

Limited data suggesting an association between exposure to overall UNGD activities and risk of childhood CNS was found in this study. See **Table 14**. Analyses revealed a significantly elevated risk of CNS in the lowest tertile of the overall UNGD activities during the primary study period, but no elevated risk estimates were observed for higher exposure levels, nor was there a dose-response relationship.

Malignant Bone Tumor and Ewing Family of Tumor

In this study, no evidence was found to support an association between exposures to UNGD activities and other environmental factors and the risk of malignant bone tumors, including EFOT. Given the small sample size of children with malignant bone tumor, particularly EFOT, additional studies with a larger sample size may be warranted.

Previous Studies

One investigation thus far (McKenzie et al., 2017) considered the association of hydraulic fracturing and the risk of childhood lymphoma and included only non-Hodgkin's lymphoma (N=50) cases which were matched to other cancer controls without "environmentally mediated" cancers.

Within a ten-mile buffer, the researchers observed no statistically significant associations between density of oil and gas development and NHL in either model, based on trend analysis across categorical IDW well counts adjusted for age, race, gender, socioeconomic status, elevation, and year of diagnosis. Of the 50 cases, 18 were unexposed and 32 were within 8 km or a five-mile buffer with UNGD activity exposure. McKenzie et al. noted odds ratios of 1.5 (95% CI; 0.72, 3.3) in the lowest tertile of exposure, 0.91 (95% CI; 0.37, 2.2) in the medium tertile, and 1.6 (95% CI; 0.77, 3.4) in the highest tertile with the closest buffer. They did, however, note an association of increased risk of Leukemia with UNGD in Colorado in ages 5-24, Acute lymphoblastic leukemia cases were 4.3 times as likely to be in the highest exposure category.

The current study team considered all forms of lymphoma (52 Hodgkin's, 22 NHL, 5 Burkitt's lymphoma, 25 miscellaneous lymphoreticular neoplasm, and 5 unspecified), and were able to consider multiple buffer distances and individual hydraulic fracturing phases as well as an overall metric that considered birth residence. In contrast, McKenzie et al. used geocoded addresses at time of cancer diagnosis as the only residence.

Lymphoma is more likely to emerge in the presence of infectious stimuli, chemical toxicity, or an immune system that has lost the ability for self-regulation (Skrabek, 2013). There are several studies investigating possible environmental risk factors for lymphoma in children and adults. Some of the environmental risk factors investigated include polychlorinated biphenyls, organophosphate and organochlorine pesticides, benzene, nitrogen dioxide, and in utero exposure to smoking. Many of these chemicals are in the IARC carcinogen list and are also found in hydraulic fracturing fluids (Mcnally, 2006). Future studies with biomarkers for exposure to UNGD activities may clarify the current study's observed association between hydraulic fracturing and risk of lymphoma.

Strengths and Limitations

This study has many strengths. It is only the second population-based study on UNGD activities and childhood cancer risk randomly sampling age, race, and sex matched controls from birth records. The study population was restricted to Western Pennsylvania counties which permitted UNGD activities since 2005. As such, the City of Pittsburgh was excluded due to a ban on hydraulic fracturing. This minimized potential confounding and bias due to other environmental risk factors. The rigid matching criteria (less than 45 days of difference in birth dates between a case and matched control) eliminated potential confounding effect by age. The collection of other environmental exposure data through publicly available sources provided additional information on factors (e.g., TRI, UMTRA, Superfund sites, impoundment ponds, compressor stations, and facilities accepting oil and gas waste), which were adjusted for through multivariable logistic models.

In addition to conventionally used well counts and IDW well counts as exposure variables, the study team was able to create a new metric called "overall activity" in estimates to evaluate cancer risk. The challenge in considering the health effects of individual hydraulic fracturing phases is that they may be occurring simultaneously in the background with other co-located wells. This overall metric accounted for the duration of UNGD activity and IDW components for each phase during the period of exposure studied. Moreover, phases of hydraulic fracturing and other potential environmental covariates including proximity to TRI, UMTRA, and Superfund sites were included in the overall analysis. An additional strength was the application of multiple buffers for proximity of residences within < 0.5, 0.5-1.0, 1-2, and 2-5 miles of these sites, which allowed for the assessment of cancer risk with UNGD proximity. The increased risk of childhood cancer with decreasing residential distance from UNGD sites suggests a probable link between UNGD activities and childhood cancer risk.

This comprehensive analysis also revealed consistent associations for various metrics of UNGD activities, which were highly correlated with each other and the risk of childhood cancer outcomes, further strengthening a probable link between UNGD activities in general and risk of childhood cancer.

This is the first study to include the four most common childhood cancers – leukemia, lymphoma, CNS tumors and malignant bone tumors. The inclusion of multiple cancer types provided a larger sample size for the study and allowed for the assessment of cancer-specific risk with UNGD activities. The strongest association was observed between UNGD activities and risk of childhood lymphoma, which are novel findings and warrant assessment by future studies.

The present study also has some limitations. The chief limitation is using distance as a proxy exposure measurement for UNGD activities. Exposure may be affected by many factors such as the nearby topography and geological formations, weather patterns, and water sources, and the behaviors of individuals residing near UNGD activity. It is possible that using distance as a proxy has resulted in exposure misclassification, which may identify an association where there is not one or vice versa. In addition, although the study team focused much attention on data cleaning and geocoding, the accuracy and completeness of the UNGD activity data used for the calculation of UNGD metrics cannot be certain. In addition, the use of residence from the birth records as a proxy for UNGD exposure from birth until index date to increase sample size also introduces the possibility of misclassification bias. However as shown in previous Table 8, there was an extremely high concordance (85%) with cases' residence at birth compared to their residence at diagnosis remaining in SW PA and an almost 80% of cases remaining in the same county. This adds validity to the use of birth certificates as a proxy for UNGD metrics for this study. Another limitation of the study was the small sample size particularly for Bone Cancer and Ewing Family of Tumor which resulted in large variations in risk estimates and wider confidence intervals.

V. Conclusion

There were no associations between unconventional natural gas development activities and childhood leukemia, brain and bone cancers, including Ewing's family of tumors. Results indicated that children who lived within 1 mile of a well had approximately 5 to 7 times the chance of developing lymphoma, a relatively rare type of cancer, compared to children who lived in a place with no wells within 5 miles. Data suggests that those who lived closer, especially in areas with greater intensity of unconventional natural gas development activities, had the highest risk. There was also a strong dose-response relationship between the overall UNGD activities over the four phases and risk of lymphoma. In addition, the closer the proximity of a residence to an UNGD site, the higher the risk of lymphoma, which further supports a possible link between UNGD activity and risk of childhood lymphoma.

For perspective, the incidence of lymphoma is, on average, 0.0012% in U.S. children under 20 years of age. Our study estimates that rate would be 0.006% to 0.0084% for children living within 1 mile of a well.

No evidence was observed for exposures to other environmental sites (i.e., TRI, UMTRA and Superfund sites), and any childhood cancers.

In this study, no evidence was found to support an association between exposures to UNGD activities and other environmental factors and the risk of leukemia, CNS tumors, and malignant bone tumors, including EFOT. Given the small sample size of malignant bone tumors, due to a very low incidence rate in the population, especially for EFOT, additional studies with a larger sample size are warranted.

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Appendices

Appendix A: Background Reference Materials

Common Hydraulic Fracturing Fluid Constituents (U.S. EPA 2015, Hurley 2015, Wollin 2020)

Additive	Common Chemical Constituents	Function
Acid	Hydrochloric acid	Cleans casing and formation prior to injection; dissolves cement, minerals, and clays to reduce clogging of pore space
Antibacterial agent/biocide	Glutaraldehyde	Controls or eliminates bacterial growth that may reduce well productivity
Breaker	Peroxydisulfuric acid diammonium salt, sodium chloride	Reduces viscosity of gels and foams and promotes recovery of fracturing fluid
Clay controller	Choline Chloride, potassium chloride	Prevents mobilization of formation clays
Corrosion inhibiter	Methanol, propargyl alcohol, isopropanol	Protects steel tubing and other equipment from corrosion
Crosslinker	Ethylene glycol, potassium hydroxide, sodium hydroxide, borate salts	Increases gel viscosity by connecting polymer molecules
Friction reducer	Hydrotreated light petroleum distillates, mineral oil	Minimizes friction when pumping fluids to optimize fluid injection
Gelling agent	Guar gum, hydrotreated light petroleum distillates	Increases fluid viscosity to promote proppant transport and reduce fluid loss
Iron controller	Citric acid	Prevents precipitation of iron compounds
pH control	Carbonic acid, dipotassium salt, potassium hydroxide, sodium hydroxide, acetic acid	Regulates pH of a solution by either inducing a change (pH adjuster) or stabilizing and resisting change (buffer) to achieve desired qualities
Scale controller	Ethylene glycol, methanol	Controls or prevents scale deposits in production conduit or completion system
Solvent	Hydrochloric acid	Controls wettability of contact surfaces or prevents or breaks emulsions
Surfactant	Naphthalene	Decrease fluid surface tension, promote injection, and fluid recovery

Appendix B: Methods Reference Materials

City of Pittsburgh Zip Codes Excluded from the Study Area

Zip code	All or part City of Pittsburgh	Zip code	All or part City of Pittsburgh	Zip code	All or part City of Pittsburgh
15106	Part City	15212	Part City	15224	All City
15120	Part City	15213	All City	15226	Part City
15201	All City	15214	Part City	15227	Part City
15203	All City	15215	Part City	15230	All City
15204	Part City	15216	Part City	15232	All City
15205	Part City	15217	All City	15233	All City
15206	All City	15218	Part City	15234	Part City
15207	All City	15219	All City	15235	Part City
15208	All City	15220	Part City	15240	Part City
15210	Part City	15221	Part City	15260	All City
15211	All City	15222	All City	15282	All City

Summary Activities for Recruitment of Controls

Mode	Number of control mothers and fathers	Number of invitations sent/calls to control mothers and fathers	Number of calls/reminders sent	Total calls/messages sent	Bounced/ spam/ duplicate	Started	Finished	Completion Rate	Response Rate
US Mail	8355	8355					357		4.3%
Email	7062	16198	32096	48294	15235	179	167	93.0%	2.4%
SMS Text	4832	8991	2612	11603	0	394	84	21.0%	1.7%
Phone follow-up	1091	831	280	1111			32		2.9%
Totals	8355	34375	34988	61008	15235	573	640	89.8%	7.7%

The Population Survey Facility (PSF) at the University of Pittsburgh assisted the research team in recruiting matched controls. Following the initial mailing to 8,355 potential controls, the PSF employed a multimode approach for recruiting controls which entailed a combination of email, text message, and follow-up phone calls. Before data cleaning and across all modes the response rate was 7.7%. Contact information was obtained from Lexis-Nexus and consisted of up to 6 emails for each control (i.e., up to 3 emails for both mothers and fathers) and 4 cell phone numbers (i.e., up to 2 for both mothers and fathers). Approximately 61,000 total calls or electronic messages were sent to recruit matched controls, resulting in 640 completed surveys prior to data cleaning.

The IRB Approval Letter

University of Pittsburgh | Institutional Review Board
Office of Research Protections

EXEMPT DETERMINATION

Date:	March 16, 2021
IRB:	STUDY21020141
PI:	Evelyn Talbott
Title:	Heath Effects of Hydraulic Fracturing
Funding:	Name: Pennsylvania Department of Health, Funding Source ID: Contract number: 4400018535
Grant Title:	None

The Institutional Review Board reviewed and determined the above referenced study meets the regulatory requirements for exempt research under 45 CFR 46.104.

Determination Documentation

Determination Date:	3/16/2021
Exempt Category:	(2)(iii) Tests, surveys, interviews, or observation (identifiable); and for which limited IRB review was conducted via expedited review

Determinations:	None
Approved Documents:	• Questionnaire, Category: Data Collection; • Attachment 1 Agency Request for Project 09-04-20_Version_0.01.doc, Category: Sponsor Attachment; • Case Brochure, Category: Recruitment Materials; • CASE PRENOTIFICATION LETTER.docx, Category: Recruitment Materials; • Control Brochure, Category: Recruitment Materials; • CONTROL PRENOTIFICATION LETTER.docx, Category: Recruitment Materials; • Exempt Application Form, Category: IRB Protocol; • Phone Call Script - Scheduling Interview, Category: Recruitment Materials; • Verbal Consent Phone Script, Category: Recruitment Materials

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Dana DiVirgilio.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

Human Research Protection Office 3500 Fifth Avenue, Suite 106 Pittsburgh, PA 15213 www.hrpo.pitt.edu

Steps for Selection of County-Matched and Non-County-Matched Controls by PADOH Bureau of Health Statistics and Registries

Step 1) Import birth data for all Pennsylvania Cancer Registry (PCR) patients eligible for this study.

Step 2) To prepare for control selection, two fields were created for every patient – "Patient_Bin_1" for resident county-matched controls and "Patient_Bin_2" for those controls not matched to resident county. "Patient_Bin_1" was created by concatenating the mother's Race, the patient's sex per the birth record, and the mother's resident County at time of the patient's birth. "Patient_Bin_2" was created by concatenating the mother's race and the patient's sex per the birth record. The mother's race as reported on the birth record was recoded as the field "Moth_Race_Bin". The following logic was used to recode the mother's race:

Mother's Reported Race ("Moth_Race" via Birth data)	Recoded Field ("Moth_Race_Bin")
White	Whi
Black/African-American	Bla
All other entries	Oth

Step 3) To create the pool of potential controls, birth records from 1990-2019 (inclusive) were imported. Due to differences in the layout of these data, three separate data sets were created based on the following years of birth: 1990-2002, 2003-2012, and 2013-2019. Births that did not occur in one of the eight counties of interest for this study were removed from the pool of potential controls. Additionally, certain birth records were removed if, based on the mother's residence zip code, the mother resided in the City of Pittsburgh at the time of the birth. Two bins were created for each potential control: "Control_Bin_1" and "Control_Bin_2". "Control_Bin_1" leveraged the same methodology as described in Step 2 to create the "Patient_Bin_1" field, and "Control_Bin_2" leveraged the same methodology as described in Step 2 to create the "Patient_Bin_2" field.

Step 4) Prior to selecting the controls, all years of birth data were combined into one data set containing the respective bins used as part of the matching criteria, a unique ID for the birth record, and the potential control's date of birth. A random number was also associated with each respective birth record for use later in the selection process. A comprehensive data set was also created for the eligible patients that only included the respective bins used as part of the matching criteria, a unique ID for the birth record, and the patient's date of birth.

Step 5) County-matched controls were identified for all patients in a single Procedure in SAS SQL (Structure Query Language) step. This initial group of record pairings, "Control Group 1", contain patient-control record pairings that were matched on sex, race, and mother's residence county (contained in the "Control_Bin_1" field). Additionally, the matching criteria also included logic to only retain record pairings where the patient's date of birth was within 45 days of the control's date of birth. Controls that matched to multiple patients were isolated, and a single patient-control pairing was selected using simple random sampling (without replacement) via the SAS procedure Proc SurveySelect. Controls identified for "Control Group 1" were sorted by the random number assigned to the respective record during Step 4. A maximum of 40 controls were selected for each patient. Final checks were made to ensure all eligible patients matched to a set of controls, verify there were no duplicate controls represented in the final data set, and determine the final frequency of patient-control pairings.

Step 6) The selection process for "Control Group 2" followed the same logic as described in Step 5 for "Control Group 1", however, controls identified in Step 5 were removed from the pool of eligible birth records prior to the selection process, and the residence county parity requirement was removed from the matching criteria. Sex, race, and date of birth proximity (i.e., controls born within 45 days of the respective patient) were leveraged during the record matching process. The sex and race fields were contained in the "Control_Bin_2" field.

Step 7) The final release files were created for the study group using the controls selected for "Control Group 1" and "Control Group 2".

Dated Summary of Protocol Modifications.

Modification	Summary	Date Approved
Pitt IRB Modification #1	Revision of consent methodology from verbal to written Addition of osteosarcoma and EFOT cases aged 20-29 (previously restricted to 0-19)	September 20, 2021
Pitt IRB Modification #2	Addition of QR code for ease of obtaining (electronic) written consent Revision of LexisNexis contract to allow for phone number and email address tracing Approval of text and email-based recruitment strategies Revision of phone call script for non-response follow-up	February 2, 2022
Pitt IRB Modification #3	Revision of survey mode from 45-60 minutes by phone to 20-25 minutes by phone or online Revision of recruitment flyer to be included in recruitment emails Inclusion of Qualtrics-based online survey link in recruitment emails	February 23, 2022
Pitt IRB Modification #4	Addition of Dr. Jean Tersak as study co-investigator Survey staff personnel updates	May 5, 2022
Pitt IRB Modification #5	Addition of paper-based residential history for eligible case families Addition of Qualtrics-based text message and email recruitment methodology Revision of postcard to indicate survey mode preference	May 16, 2022
Pitt IRB Modification #6	Approval of Dr. Jean Tersak's letter of support for case recruitment materials Approval to host in-person informational sessions for eligible case families at State Health Centers	June 6, 2022
Pitt IRB Modification #7	Revision of Control Incentive to $15; Updated verbiage to reflect shortened survey length (20-25 min)	July 22, 2022
DOH IRB Modification #1	Verbal consent approved for cases and controls (double check)	August 21, 2022

Timeline of Study Activities

Action	Date
DOH Contract Effective Date	September 1, 2020
Study activities commenced by Pitt Study Team (kick-off meeting)	November 20, 2020
Study funding received by Pitt Public Health	December 8, 2020
Initial Pitt IRB Submission	February 23, 2021
Pitt IRB Approval	March 16, 2021
DOH Protected Use Agreement submission	April 19, 2021
Initial DOH IRB submission	June 14, 2021
DOH IRB Approval	June 17, 2021
DOH Protected Use Agreement Approval	July 7, 2021
External Advisory Board Inaugural Meeting	August 5, 2021
Initial case dataset received from DOH (survivors only)	September 2, 2021
Pitt IRB Modification #1 Approval	September 20, 2021
LexisNexis Contract Finalized	September 21, 2021
Case recruitment period commenced	September 28, 2021
Conclusion of 1st quarter of recruitment efforts: n= 71 case interviews	December 31, 2021
Revised case dataset received from DOH includes corrected classification of cancer cases)	January 15, 2022
Pitt IRB Modification #2 Approval	February 2, 2022
Pitt IRB Modification #3 Approval	February 23, 2022
Revised case dataset received from DOH (includes decedents)	February 25, 2022
Conclusion of 2nd quarter recruitment efforts: n= 107 case interviews	March 31, 2022
Complete control dataset received from DOH	April 21, 2022
Pitt IRB Modification #4 Approval	May 5, 2022
Pitt IRB Modification #5 Approval	May 16, 2022
Control recruitment period commenced	May 18, 2022
Pitt IRB Modification #6 Approval	June 6, 2022
Conclusion of 3rd quarter of recruitment: n= 140 case interviews, n=126 control interviews	June 30, 2022
Pitt IRB Modification #7 Approval	July 22, 2022
SMS text message recruitment of control families commenced	September 8, 2022
Email recruitment of control families commenced	September 14, 2022
Electronic recruitment of control families (Emails and Texts) done	September 22, 2022
Conclusion of 4th quarter of recruitment efforts: n= 234 case interviews, n= 640 Controls in	September 27th, 2022
Case/control recruitment period closure	September 27th, 2022
Data cleaning phase commencement	August 2022
Data cleaning phase closure: n= 234 case interviews, n= 373 Control interviews	October 2022
Data analysis phase commencement	September 2022
Data analysis phase closure	October 2022
Report writing phase commencement	October 2022
Report writing phase complete	November 2022
Report 1A submitted to DOH, Report 1B submitted to DOH	11/16 &11/23 2022
Final report submitted to DOH	March 1, 2023

Geocoding Addresses

Addresses of cases and controls were geocoded in ArcMap 10.6, using ArcGIS World Geocoding Service (WCS). All addresses were matched to a set of geocoordinates. WCS included a percentage of accuracy for each match that it found. A decrease in percentage could be due to a typo in the address such as “Street” versus “Avenue” or a misspelling of street name. Sometimes WCS returned a match for a street, but the number provided by the participant was not a currently recognized address along with that street. WCS then identified the centroid of the street. Lastly, it was possible that WCS was not able to find a street with the same name that matched the city and zip code. In that case, WCS defaulted to selecting the centroid of the zip code. In some scenarios, WCS finds multiple potential matches with varying levels in the percentage of accuracy. The analyst can review these other potential matches and evaluate if another one could fit better to the information provided by a participant. If an alternative match was better, the analyst can manually match that set of geocoordinates instead of what was originally selected by WCS. If the other options are less well fitting, the analyst keeps the match the same.

A total of 892, or 78%, of addresses were matched with 100% accuracy, and 257 of the remaining addresses had certainty scores below 100%. However, upon review of these 257, 163 addresses were correctly matched to point addresses. In these instances, typos or inclusions of unit numbers, etc. caused a decrease in the accuracy percentage, but the correct point was identified. Of the remaining addresses with accuracy below 100%, 74 were matched to the centroid of the street and 19 used a zip code centroid where no street could be identified. Only 6 of the centroid addresses were manually rematched with a potential match not originally selected by WCS. In all other cases, the analyst agreed with the choice of geocoordinate selected by WCS. Once the review was done, the geocoding results were exported into a csv file to be uploaded to GCP to the data programmer for exposure metrics calculation. ArcMap was not used to calculate the IDW exposure metrics due to the computing power required to measure distances between all houses and wells.

Aggregating Exposure Metrics Across Residential History

To have a dataset representing individual participants as opposed to houses, exposure metrics were then aggregated across residences for each case and control. Metrics were first calculated by house and by time period as described above. Inverse distance weighted metrics were then summed across houses for all time periods.

Since IDW Well counts cannot appropriately be summed across residences, as this would artificially inflate the counts of individuals who moved often, a different method was used for aggregation. Proportions were calculated for time spent in each individual house as part of the total time period of all residences listed per person. IDW well counts were multiplied by the proportion and then summed to get a time-weighted sum of wells for each person and time period. This potential inflation only occurs with this IDW well count variable but would not occur with the other metrics as they include a duration element. This is how the additional metrics calculated in this study improve upon metrics in the existing literature. For the other environmental exposure variables, the same procedure was used.

Addressing Issues with Incomplete Data

The study team anticipated incomplete data in exposure metrics and well data for the entire exposure period. To address these issues, the following protocol was used:

- For gaps in residency: If residency or well data were missing for some of the exposure period, the metric was based on available data. For each metric computed, a companion variable was calculated indicating the proportion of the time period with available data (variable name: data completeness). For example, the value ranges from 0 to 1 (depending on the proportion of residential history provided), a value of 1 indicates data was provided for the 100% of the participant's time period, while a value of 0.94 indicates data residential history was provided for 94% of the participant's time period. In the complete analysis, only 7 of 213 cases and 7 of 213 controls had less than 100% completion. A sensitivity analysis found that excluding these pairs did not change the results.
- For study participants who relocated to residences outside the eight-county study area: A buffering zone of 5 miles from all borders of the eight-county study area extending into the surrounding counties has been considered when downloading exposure data. Data within the buffering zone or of the adjacent counties that the buffering zone was in were downloaded.
- For study participants who relocated outside of the study area and its buffering area to another hydraulic fracturing county within Pennsylvania: DEP data was used to determine if the participant lived within ten miles of an area with hydraulic fracturing. If the participant lived within an area where hydraulic fracturing occurred, their exposure was considered unknown for that residence, which is accounted for in the data completeness variable described above. Residential histories for study participants who relocated outside of the study area and its buffering area to other states with hydraulic fracturing (West Virginia, Ohio, Texas, etc.) were flagged based on whether a hydraulic fracturing timeline and estimated exposure was able to be shown. If unable to be shown we their exposure was considered to be unknown for that residence, which is accounted for in the data completeness variable described above.
- Residential histories for study participants who relocated outside of the study area and its buffering area to other states without hydraulic fracturing were considered to have no exposure to hydraulic fracturing.
- For missing date information:
    - If the day of the month was missing: the 15th of the month was used
    - If the month was missing: the 7th month and 1st day was used
    - If the end date (move-out date) for a residence was missing: the date 1 day prior to the next listed residence was used
- For missing GIS information which could not be resolved to house number and street name:
    - If data had only street name, GIS coordinates corresponding to the centroid of the street were used
    - If data had only town/city, GIS coordinates corresponding to centroid of town/city used
    - If data had only zip code, GIS coordinates corresponding to centroid of zip code used

Appendix C. Outreach and Subject Recruitment Materials

Letter from the Secretary of Health

COMMONWEALTH OF PENNSYLVANIA
OFFICE OF THE SECRETARY OF HEALTH

The University of Pittsburgh Graduate School of Public Health is collaborating with the Pennsylvania Department of Health in conducting valuable research into the possible environmental risk factors for childhood cancer including exposures related to Hydraulic Fracturing in SW PA. Childhood cancer is the third leading cause of death for those under age nineteen.

To complete this research, the University must compare interview and environmental exposure information between children who have been diagnosed with cancer with data on those who have not. The cancer-free group is referred to as "controls" while those with cancer are referred to as "cases" for this type of study. The University is asking your assistance in this important study.

Parents of children with cancer will be identified through the Pennsylvania Cancer Registry as being diagnosed with this condition between 2010-2019, and parents of control children were identified from a sample of Pennsylvania birth records (by county) which were then selected by birth year and matched by gender and race with a child with cancer.

Participation in this study is entirely voluntary, and if you do not wish to be contacted again, simply return the enclosed card with the "NO" box checked. However, I encourage you to give serious consideration to participating in this valuable research. We need studies such as this one to find the possible causes and risk factors for childhood cancers. Your participation in this study will serve as a small but very personal contribution in helping to find the risk factors for childhood cancer, leading to possible improvements in the lives of others.

If you have any questions about the study, please contact Dr. Evelyn O. Talbott, DrPH, MPH, at 412-624-3074. For any information related to the opt-out option that cannot be answered by the University study team, you may call the Pennsylvania Department of Health at 717-783-2548.

Thank you in advance for considering participation in this important study.

Sincerely,

Denise Johnson, MD
Acting Secretary and Physician General
Pennsylvania Department of Health

Case Letter from the Pitt Study Team

University of Pittsburgh

pennsylvania
DEPARTMENT OF HEALTH

PA Health and Environment Study

ENROLL ONLINE using this QR code!

June 1, 2022

STUDYID####

Dear Ms. and Mr ,

We are asking *the parents of children who were diagnosed with cancer* to participate in the PA Health and Environment Study. The study is a *one-time online OR telephone survey* examining possible environmental risk factors of childhood cancer including hydraulic fracturing. This study was initiated by the PA Department of Health in response to community concerns about environmental exposures. A letter from the PA Acting Secretary of Health, and a brochure explaining the study is enclosed.

We need your help to make this study representative. Your residential history may be the key to understanding the environmental determinants of health. After your participation in this one-time 20 minute online OR telephone survey, you will receive a *$25 payment card* as compensation for your time.

To enroll or decline participation, you can scan the QR code above or navigate to the link paenv.pitt.edu/enroll, which will take you to an online enrollment and survey form. OR if you prefer, you can return the postcard enclosed here, and we will contact you to take the survey.

If you have any questions email me at eot1@pitt.edu or paenv@pitt.edu. My office phone number is 412-624-3074; and our project office phone number is 412-648-5185. You can read more about the study at paenv.pitt.edu/ccs.html.

Thank you so much for your consideration of this important request.

Evelyn Talbott

Jian-Min Yuan

Evelyn O. Talbott, DrPH, MPH
Professor, Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Jian-Min Yuan, MD, PhD
Professor, Department of Epidemiology
UPMC Hillman Cancer Center, University of Pittsburgh
Arnold Palmer Endowed Chair-Cancer Prevention

Control Letter from the Pitt Study Team

University of Pittsburgh

pennsylvania
DEPARTMENT OF HEALTH

PA Health and Environment Study

ENROLL ONLINE using this QR code!

July 1, 2022 **STUDYID ######**

Dear Ms. and Mr.,

We are asking *the parents of children who were **NOT** diagnosed with cancer* to participate in the PA Health and Environment Study. The study is a *one-time online survey* examining possible environmental risk factors of childhood cancer including hydraulic fracturing. This study was initiated by the PA Department of Health in response to community concerns about environmental exposures. A letter from the PA Secretary of Health and a brochure explaining the study is enclosed.

We need your help to make this study representative. Your residential history may be the key to understanding the environmental determinants of health. After your participation in this one-time 20-minute online survey, you will receive a *$15 payment card* as compensation for your time.

To enroll or decline participation, you can scan the QR code above or navigate to the link paenv.pitt.edu/enroll, which will take you to an online enrollment and survey form.

If you have any questions email me at eot1@pitt.edu or paenv@pitt.edu. Dr. Talbott's office phone number is 412-624-3074; and our project office phone number is 412-648-5185. You can read more about the study at paenv.pitt.edu/ccs.html.

Thank you so much for your consideration of this important request.

Evelyn O. Talbott, DrPH, MPH
Professor, Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Jian-Min Yuan, MD, PhD
Professor, Department of Epidemiology
UPMC Hillman Cancer Center, University of Pittsburgh
Arnold Palmer Endowed Chair-Cancer Prevention

Opt-In/Opt-Out Postcard

Please check the statement that represents your decision about participation in this study and sign and date at the bottom:

☐ I **DO** wish to be contacted regarding this study.

If yes, please fill out the contact information below:

Signature: ______________________________ Date: ___/___/20____

Name: ____

Email: ____

Phone Number: ____

Survey preference (check one): Text ___ Online ___ Phone ___

Current Address: ____

☐ I **DO NOT** wish to be contacted regarding this study.

Signature: ______________________________ Date: ___/___/20____

Name: ____

Please return this card in the envelope that has been supplied.

Research ID: _____________

Case Brochure

Why is this research being done?

Childhood cancer is the third leading cause of death in US children, yet there are very few known risk factors.

Pitt Public Health is conducting this study to consider some of the risks that may play a role. These include lifestyle behaviors, residential history, family medical history, workplace and environmental exposures, and other exposures during childhood and early life.

University of Pittsburgh
Graduate School of Public Health
Department of Epidemiology
130 DeSoto Street
Pittsburgh, PA 15261

paenv.pitt.edu

Case Control Study: Childhood Cancer in Southwestern Pennsylvania

Recruiting Parents for an Important Study

Please see why inside!

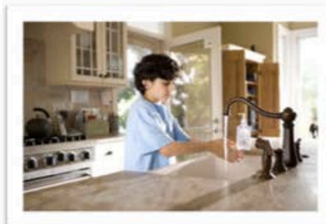
University of Pittsburgh

How did we get your name?

- Information was obtained through the Pennsylvania Cancer Registry as well as from PA birth records (by county) from the Department of Health.

Participation is voluntary!

- If you do choose to participate:
  - This will not impact your access to healthcare or treatment
  - You can withdraw from the study at any time



Who will be asked to participate in this research study?

Parents who have a child:

- Who was diagnosed with Ewing's/ bone cancers at age 0-29 years during 2010 through 2019, or
- Who was diagnosed with Childhood Leukemia, Lymphoma and Central Nervous System tumors at age 0-19 years during 2010 through 2019
- Resided in one of the following Pennsylvania counties:
  - **Allegheny County**
  - **Armstrong County**
  - **Beaver County**
  - **Butler County**
  - **Fayette County**
  - **Greene County**
  - **Washington County**
  - **Westmoreland County**

What will parents be asked to do?

- Complete a one-time, 45-60 minute telephone interview
  - Includes questions about individual, occupational, and environmental exposures
- Your time will be compensated

Other Information

- We will only be speaking with parents
- Any information provided for this research study will be confidential

Contact Information

Evelyn O. Talbott, DrPH, MPH
Principal Investigator

- **Phone:** (412) 648-5185
- **Email:** paenv@pitt.edu
- **Website:** paenv.pitt.edu
- **Project Office Location:**
  University of Pittsburgh
  Graduate School of Public Health
  A545 Public Health Building,
  130 De Soto St
  Pittsburgh, PA 15261

Control Brochure

Why is this research study being done?

Childhood cancer is the third leading cause of death in US children, yet there are very few known risk factors.

Pitt Public Health is conducting this study to consider some of the risks that may play a role. These include lifestyle behaviors, residential history, family medical history, workplace and environmental exposures, and other exposures during childhood and early life.

University of Pittsburgh
Graduate School of Public Health
Department of Epidemiology
130 DeSoto Street
Pittsburgh, PA 15261

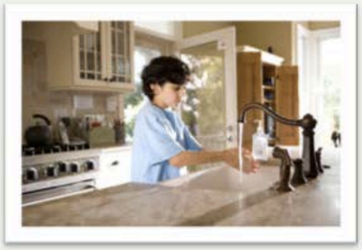
paenv.pitt.edu

Case Control Study: Childhood Cancer in Southwestern Pennsylvania

Recruiting Parents of Children Without Cancer as Controls for an Important Study

Please see why inside!

University of Pittsburgh



How did we get your name?

- Information was obtained from the PA birth records (by county) from the Department of Health.
- The participants in both groups must be matched in the following categories: **Age, Sex, Race, and County**.

What will parents be asked to do?

- Complete a one-time, 45-60 minute telephone interview
  - ◊ Includes questions about individual, occupational, and environmental exposures
- Your time will be compensated

Why are we asking you to participate in this study?

- We are recruiting a control group—families of children without cancer—to compare to families of children with this condition.
- Participation in this study will serve as an important and personal contribution in helping identify risk factors for childhood cancer.

- **Participation in this study is limited to the following counties:**
  - ◊ **Allegheny County**
  - ◊ **Armstrong County**
  - ◊ **Beaver County**
  - ◊ **Butler County**
  - ◊ **Fayette County**
  - ◊ **Greene County**
  - ◊ **Washington County**
  - ◊ **Westmoreland County**

Other Information

- We will only be speaking with parents
- Any information provided for this research study will be kept strictly confidential

Participation is voluntary!

- If you do choose to participate, you can withdraw from the study at any time

Contact Information

Evelyn O. Talbott, DrPH, MPH
Principal Investigator

- **Phone:** (412) 648-5185
- **Email:** paenv@pitt.edu
- **Website:** paenv.pitt.edu
- **Project Office Location:**
  University of Pittsburgh
  Graduate School of Public Health
  A545 Public Health Building,
  130 De Soto St
  Pittsburgh, PA 15261

Recruitment Text Message Scripts

Text Message Enrollment Scripts

Script 1 (briefest, requires no interaction with study team):
Header: **Pitt Public Health Needs Your Help.**
Important study on childhood cancer and hydraulic fracturing in SW PA!
Brief online survey, click here to consent and enroll: paenv.pitt.edu/enroll
$25 dollars for your time.
Reply NO to decline.

Script 2 (brief, requires no interaction with study team):
Header: **Pitt Public Health Needs Your Help.**
Hi (participant)! This is (staff) at Pitt Public Health. We're trying to reach you regarding a childhood cancer case-control survey. If you haven't already, will you consider participating in our brief, online survey? You will receive $25 for your time.
Here is the link to consent and enroll: paenv.pitt.edu/enroll
Reply NO to decline enrollment.

Script 3 (extended, requires interaction with study team):
Header: **Pitt Public Health Needs Your Help.**
Hi, this is Dr. Talbott's study team at the University of Pittsburgh School of Public Health. We are trying to contact Mr./Ms. _____ regarding a childhood health study. Do we have the right person? Reply YES or NO to decline.

No – Thank you, have a nice day.
Yes – We had sent a letter to him and wanted to confirm that he received it. The first letter was sent on date and the second letter was sent on date. Can you confirm that you received these letters? Reply YES or NO.

No, I did not receive the letters.

If you would like information about this study or would like to enroll, you can do so at paenv.pitt.edu/enroll

Yes, I received the letters.

That's great. As you know, we are studying the risk factors for childhood cancer, which we know very little about. Your participation would allow us to make accurate conclusions and help prevent childhood cancer in the future. You would receive $25 for the one-time online survey. Would you be interested in participating? Reply YES or NO to decline.

No, I would not like to participate.

Thanks for your response. Have a nice day.

Yes, I would like to participate.

Thank you! You can enroll online at paenv.pitt.edu/enroll

Recruitment Letter from Dr. Tersak

UPMC | CHILDREN'S
HOSPITAL OF PITTSBURGH

Hematology/Oncology
Survivorship

Children's Hospital Drive
4401 Penn Avenue
Pittsburgh, PA 15224
T 412-692-8570
F 412-692-3412
SurvivorConnect@chp.edu

www.chp.edu/survivorship

Dear Mr. and Mrs.:

I am writing to you regarding an important study at the University of Pittsburgh, the "PA Health and Environment Study." I was asked to be involved due to my work as a pediatric oncologist. This study has the potential to help answer critical questions concerning environmental exposures within Southwestern Pennsylvania. A large number of participants from our region will increase the likelihood that we are able to answer the important questions of this study.

As the enclosed brochure describes, Pitt Public Health, in partnership with the Pennsylvania Department of Health, is conducting a case-control study of environmental risk factors and childhood cancer. Studies like this are necessary to evaluate the impact of industrial activities, including hydraulic fracturing ("fracking") on human health, especially on children's overall health and cancer risk.

I am writing to you in support of this state funded study and to encourage you to please consider participating when you are contacted by the Pitt study team. Participation in this study would require you to complete a short survey regarding your residential history, done over the phone or online, and should take approximately 20 minutes. When your answers are aggregated together with more than 1,000 participants like you, we can conduct detailed analysis and learn if the industrial activities are related to childhood cancer. Such knowledge is crucial for the development of strategies to mitigate or even eliminate such environmental risk factors in our community and beyond.

Your participation will be a critical contribution to advancing our understanding of pediatric cancer's environmental origins. I thank you in advance for your consideration to participate. Please reach out to the study team or directly to me if you have any questions about the study.

Sincerest thank you,

Jean M Tersak

Jean M Tersak, MD

Eventbrite Email Invitation

University of Pittsburgh

pennsylvania

PA Health and Environment Study

Hello!

The University of Pittsburgh study team is hosting two informational sessions for parents who are eligible to participate in a paid survey for the PA Health and Environment Study. You can read more about the study at paenv.pitt.edu/ccs.html.

These informational sessions will be held on:

Wednesday, August 10th from 9-11 AM
Westmoreland County's State Health Center,
233 W. Otterman St
Greensburg, PA 15601

and

Friday, August 12th from 1-3 PM
Washington County's State Health Center,
167 N. Main St., Suite 100
Washington, PA 15301

If you would like to attend, we kindly ask that you RSVP online
by Sunday, August 7th with a free ticket
using password **PAENV**
You can RSVP for the Westmoreland session here:
https://www.eventbrite.com/e/393175698097
or the Washington session here:
https://www.eventbrite.com/e/393191595647

If you have any questions email the study team at paenv@pitt.edu or call (412) 648-5185.

Thank you so much for your time and we hope to see you at the informational session.

Evelyn Talbott

Evelyn O. Talbott, DrPH, MPH
Professor, Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Jian-Min Yuan

Jian-Min Yuan, MD, PhD
Professor, Department of Epidemiology
UPMC Hillman Cancer Center, University of Pittsburgh
Arnold Palmer Endowed Chair-Cancer Prevention

2-Page Residential Questionnaire

ID Number ________

I consent to participate in the Pennsylvania Health and Environment Study:

Name: _______________________Signature: ____Date___________

Re(child's name)_ ______, please list your residences one year before your child was conceived _________through (date DX)___________

Email: ____--

Address of Residence: Street Address and City/Town	Zip Code	Move-in Date (Month & Year)	Move-out Date (Month & Year)	Was home within 1 mile of at least one major industrial facility? (check one)	Was there any oil/ gas activity or facility nearby? (check one)	Was this home within 1 mile of a farm/agricultural facility? (check one)
1.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type (ex: dairy farm, apple orchard, etc.)
2.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know__	Yes_____ No___ Unknown_____ If yes: please describe type
3.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type
4.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type
5.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type

Regarding (child's name)_________, please list your residences from one year before your child was conceived through (date)________

Address of Residence: Street Address and City/Town	Zip Code	Move-in Date (Month & Year)	Move-out Date (Month & Year)	Was home within 1 mile of at least one major industrial facility? (check one)	Was there any oil/ gas activity or facility nearby? (check one)	Was this home within 1 mile of a farm/agricultural facility? (check one)
6.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type (ex: dairy farm, apple orchard, etc.)
7.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type
8.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type
9.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type
10.				Yes___ No__ Unknown__ If yes, describe:	Yes___ No__ Unknown__ If Yes, approx. date you noticed activity ___/___/___ or Don't Know __	Yes_____ No___ Unknown_____ If yes: please describe type

Appendix D. Medium-Length Qualtrics Survey (20-25 min)

SWPA Child Cancer - Shortened

Thank you, for participating in our study.

Childhood Cancer is the third leading cause of death among children in the US and yet there are very few known risk factors. This study will examine some risks that may play a role. These include environmental exposures, residential history, and lifestyle behaviors during childhood and early life. You will receive $25 for your time completing the survey. If there are any questions that you are uncomfortable about, you may decline to answer at any time.

Please do not hesitate to contact our project office at 412-648-5185 or email paenv@pitt.edu, if you have any questions.

1. What is your full name?

First Name ____
Last Name ____

2. **What is your child's name? This is your child that was diagnosed with cancer between** the ages of 0-29, in the years of 2010**-2019.**

First Name ____
Last Name ____

3. If you remember your four digit study ID number included in our enrollment materials please enter it here. ____________________________

4. What is your relationship to the child?

a) Biological Mother
b) Biological Father
c) Step Mother
d) Step Father
e) Other ____

5. What is the child's date of birth? ___________________________

6. Confirm your child's gender.

a) Male
b) Female
c) Child is Non-binary/third gender
d) Prefer not to say

7. Would you describe the child as being of Hispanic origin?

a) Yes

b) No
c) Unknown

8. Which of the following terms best describes the child's racial background? Check all that apply.

a) White
b) Black or African American
c) Native American/American Indian or Alaska Native
d) Asian or Pacific Islander
e) Other ______________________________
f) Unknown

9. Now we would like to ask what daycares and schools the child has attended, beginning with their first daycare or school and continuing in order:

Please include ANY address outside the home where the child spent long periods of time during the day.

	Name of School or Daycare	Year Attended - From YEAR to YEAR		School or Daycare Address			
	Name of Daycare or School	Year Start	Year End	Street	City	State	Zip
Daycare / School 1							
Daycare / School 2							
Daycare / School 3							
Daycare / School 4							
Daycare / School 5							
Daycare / School 6							
Daycare / School 7							
Daycare / School 8							

MOTHER'S BACKGROUND

10. What was the highest grade or year of school you / the mother had completed at the time that the child was born?

a) No formal schooling
b) Less than high school
c) 12 years, completed high school or equivalent
d) 1-3 years of college
e) Completed technical college
f) Associates degree
g) 4 years of college or Bachelors degree
h) Advanced degree
i) Don't know

11. What was your / the mother's marital status at the time the child was born?

a) Married or living with partner
b) Separated
c) Divorced
d) Widowed
e) Never married and not living with partner
f) Other ____

FATHER'S BACKGROUND

12. What was the highest grade or year of school you / the father had completed at the time that the child was born?

a) No formal schooling
b) Less than high school
c) 12 years, completed high school or equivalent
d) 1-3 years of college
e) Completed technical college
f) Associates degree
g) 4 years of college or Bachelors degree
h) Advanced degree
i) Don't know

13. What was your / the father's marital status at the time the child was born?

a) Married or living with partner
b) Separated
c) Divorced
d) Widowed
e) Never married and not living with partner
f) Other ____

RESIDENTIAL HISTORY

How many residences did you live in starting from one year before the conception of the child and ending with the date of the child's first cancer diagnosis?

14. How many residences did the biological mother live in starting from one year before the conception of the child and ending with the date of the child's first cancer diagnosis? ______________________________

15. How many residences did you live in starting from one year before the conception of the child and ending with the date of the child's first cancer diagnosis?

	Residences					Approximate Move-IN Date		Approximate Move-OUT Date	
	Street Address	City/Town	State	ZIP	County	Move-IN Month	Move-IN YEAR	Move-OUT Month	Move-OUT YEAR
Address 1 (starting 1 Year BEFORE CONCEPTION)									
Address 2									
Address 3									
Address 4									
Address 5									
Address 6									
Address 7									
Address 8									
Address 9									
Address 10									

Now we are going to ask question about your house at Address 1.

16. What year was this residence built? ______________________________

17. Which PRIMARY FORM of heating fuel do/did you use at this residence? (choose all that apply)

a) Natural Gas
b) Electricity
c) Propane
d) Kerosene
e) Wood
f) Coal
g) Solar
h) Don't know

18. What type of air conditioning did you use at this residence?

a) Central air conditioning
b) Window/wall air conditioning units
c) No air conditioning
d) Other - Please describe ___________________________________
e) Don't know

19. Did you or a family member/other resident operate a business out of this home, such as an auto mechanic shop or hair salon?

a) Yes (Please describe business) ________________________________
b) No

c) Don't know

I am now going to ask you some questions about pesticide, herbicide, and insecticide use for your residence at Address 1.

20. Was this residence ever exterminated for insects and pests so that you had to leave the house for a few hours?

a) Yes
b) No
c) Don't know

Display This Question:

If: Was this residence ever exterminated for insects and pests so that you had to leave the house for... = Yes

21. How often was this residence treated for pests?

a) Once a week
b) Once a month
c) Once every 2-3 months
d) Once a year
e) Don't know
f) Other, please specify ____

22. Was the yard or garden around this residence ever treated with insecticides or herbicides to control insects or weeds?

a) Yes
b) No
c) Don't know

Display This Question:

If: Was the yard or garden around this residence ever treated with insecticides or herbicides to cont... = Yes

23. How often was this yard or garden treated for pests?

a) Once a week
b) Once a month
c) Once every 2-3 months
d) Once a year
e) Don't know
f) Other, please specify ____________________________________

24. What was the primary source of water for drinking and cooking at this residence? Please check all that apply:

a) City or township water supply
b) Well
c) Bottled water (for cooking and drinking only, not for showering)
d) Don't know

25. Did you ever have your water tested at this residence?

a) Yes
b) No
c) Don't know

26. Did you ever have this residence tested for radon?

a) Yes
b) No
c) Don't know

27. Did this residence ever require radon remediation?
a) Yes
b) No
c) Don't know

Display This Question:

If: Did you ever have this residence tested for radon? = Yes

28. If you can recall, what were the approximate levels of radon detected?
____

29. Did this residence have an attached garage?

a) Yes
b) No
c) Don't know

I am now going to ask you some questions about the proximity of Address 1 to some facility types.

30. Was this residence located within 1 mile of a MAJOR INDUSTRIAL FACILITY?
Examples of these are: a factory, agricultural site or farm, power plant, steel mill, cement factory, chemical plant, etc.

a) Yes
b) No
c) Don't know

Display This Question:

If was this residence located within 1 mile of a MAJOR INDUSTRIAL FACILITY? = Yes

31. Were there more than one MAJOR INDUSTRIAL facility within 1 mile of this residence?

a) Yes. If yes, how many? ____
b) No
c) Don't know

Display This Question:

If was this residence located within 1 mile of a MAJOR INDUSTRIAL FACILITY? = Yes

32. If YES, can you describe all of these facilities?
____

33. Was this residence located within 1 mile of any OIL & GAS ACTIVITY or FACILITY

a) Yes
b) No
c) Don't know

Display This Question:

If Loop current: Was this residence located within 1 mile of any OIL & GAS ACTIVITY or FACILITY... = Yes

34. Was there considerable noise at this residence due to OIL & GAS ACTIVITIES?

a) Yes
b) No
c) Don't know

Display This Question:

If Loop current: Was this residence located within 1 mile of any OIL & GAS ACTIVITY or FACILITY... = Yes

35. Did you or any of your household members notice excessive dust generated from the OIL & GAS ACTIVITIES?

a) Yes
b) No
c) Don't know

36. Was this residence located within 1 mile of a FARM or AGRICULTURAL facility?

a) Yes
b) No
c) Don't know

Display This Question:

If Loop current: Was this residence located within 1 mile of a FARM or AGRICULTURAL facility? = Yes

37. Did you or any of your household members notice excessive dust, noise, odors, or other irritants generated from the agricultural activities that impacted your daily quality of life? ____

MOTHER'S OCCUPATIONAL HISTORY

How many jobs did you/the mother have in the period starting one year before the conception of the child and ending 2 years after the child's birth.

38. During the year before you were/the mother was pregnant with the child, did you work outside of the home?

a) Yes
b) No
c) Other ____________________________________

39. How many jobs did you / the Mother have in the period starting one year before the conception of the child and ending 2 years after the child's birth. _______________

Please tell me all of the different jobs you/the mother had outside of the home during this period - from 1 year before conception to 2 years post the birth of the child.

Please give the job title and month and year when you started and stopped working at that job.

40. How many jobs did you/the mother have in the period starting one year before the conception of the child and ending 2 years after the child's birth.

	Job Title	Date Started		Date Stopped	
	Job Title	Month	Year	Month	Year
Job 1					
Job 2					
Job 3					
Job 4					
Job 5					
Job 6					
Job 7					
Job 8					
Job 9					
Job 10					

41. For the first job you listed – as first job title, which of these categories are most similar to your occupational category?

11 = Agriculture, Forestry, Fishing and Hunting ... Refused

42. For the first job you listed - as first job title, which of these occupations are most similar to your occupation?

1 = Accountant, auditor, or bookkeeper... Refused

Display This Question:

If For the first job you listed -- as first job title, which of these occupations a... = 27 = Other (specify):

43. You said "Other" for job title. Please specify: ______________________________

For the first job you listed - - as first job title, - please answer the questions below.

44. Did/do you/the mother work at this job part time or full time?

a) Part time
b) Full Time
c) Don't Know

45. Did you/the mother continue to work at this job while pregnant?

a) Yes
b) No
c) Don't Know

46. If you were / the mother was at this job at the time you gave birth, did you / the mother take maternity leave?

d) Yes
e) No
f) Don't Know

Now I would like to ask you more about the chemicals or substances that you/the mother may have used at work. Some of the names may not sound familiar to you, but please answer as best you can.

47. Did you/the mother work with any of the following materials?

	Did you work with these?			[IF YES} Were you working with them during preconception or pregnancy?	
	Yes	No	Don't Know	Pre-conception	Pregnancy
1. Adhesives or glues, like rubber cement	○	○	○	☐	☐
2. Alcohols, such as methanol or ethanol, formaldehyde	○	○	○	☐	☐
3. Anesthetic gases	○	○	○	☐	☐
4. Automotive fluids, such as antifreeze, brake fluid, degreasers, freon, gasoline	○	○	○	☐	☐
5. Benzene	○	○	○	☐	☐
6. Volatile organics, such as: carbon disulfide, carbon tetrachloride, diesel fumes, ethylene oxide, glycol ethers, styrene, toluene, trichloroethylene (TCE) or trichlorethane (TCA), xylene	○	○	○	☐	☐
7. Metals, such as: chromium, lead, manganese, nickel, metal dust or fules	○	○	○	☐	☐
8. Paint products, such as: oil-based paints, paint strippers, paint thinners, lacquers	○	○	○	☐	☐
9. Pesticides, herbicides, fungicides, or insecticides	○	○	○	☐	☐
10. Pharmaceuticals or drugs	○	○	○	☐	☐
11. Phthalates	○	○	○	☐	☐
12. Vinyl chloride	○	○	○	☐	☐
13. X-ray or radioactive materials	○	○	○	☐	☐
14. Hair dyes	○	○	○	☐	☐
15. Any other? ________	○	○	○	☐	☐

FATHER'S OCCUPATIONAL HISTORY

How many jobs did you / the father have in the period starting one year before the conception of the child and ending 2 years after the child‘s birth.

Please tell me all of the different jobs you/the father had outside of the home during this period - from 1 year before conception with the child to 2 years after the birth of the child.

48. Please give the job title and month and year when you/ the father started and stopped working at that job.

	Job Title	Date Started		Date Stopped	
	Job Title	Month	Year	Month	Year
Job 1					
Job 2					
Job 3					
Job 4					
Job 5					
Job 6					
Job 7					
Job 8					
Job 9					
Job 10					

49. For the first job you listed – as first job title, which of these categories are most similar to your occupational category?

11 = Agriculture, Forestry, Fishing and Hunting ... Refused

50. For the first job you listed - as first job title, which of these occupations are most similar to your occupation?

1 = Accountant, auditor, or bookkeeper... Refused

Display This Question:

If For the first job you listed -- as first job title, which of these occupations a... = 27 = Other (specify):

51. You said "Other" for job title. Please specify: ____________________________________

For the first job you listed - - as first job title, - please answer the questions below.

52. Did/do you/the father work at this job part time or full time?

a) Part time
b) Full Time
c) Don't Know

Now I would like to ask you more about the chemicals or substances that you/the father may have used at work. Some of the names may not sound familiar to you, but please answer as best you can.

53. Did you/the father work with any of the following materials?

	Did you work with these?			[IF YES} Were you working with them during preconception or pregnancy?	
	Yes	No	Don't Know	Pre-conception	Pregnancy
1. Adhesives or glues, like rubber cement	○	○	○	☐	☐
2. Alcohols, such as methanol or ethanol, formaldehyde	○	○	○	☐	☐
3. Anesthetic gases	○	○	○	☐	☐
4. Automotive fluids, such as antifreeze, brake fluid, degreasers, freon, gasoline	○	○	○	☐	☐
5. Benzene	○	○	○	☐	☐
6. Volatile organics, such as: carbon disulfide, carbon tetrachloride, diesel fumes, ethylene oxide, glycol ethers, styrene, toluene, trichloroethylene (TCE) or trichlorethane (TCA), xylene	○	○	○	☐	☐
7. Metals, such as: chromium, lead, manganese, nickel, metal dust or fules	○	○	○	☐	☐
8. Paint products, such as: oil-based paints, paint strippers, paint thinners, lacquers	○	○	○	☐	☐
9. Pesticides, herbicides, fungicides, or insecticides	○	○	○	☐	☐
10. Pharmaceuticals or drugs	○	○	○	☐	☐
11. Phthalates	○	○	○	☐	☐
12. Vinyl chloride	○	○	○	☐	☐
13. X-ray or radioactive materials	○	○	○	☐	☐
14. Hair dyes	○	○	○	☐	☐
15. Any other? ______	○	○	○	☐	☐

MOTHER'S SMOKING HISTORY

54. Have you/ has the mother smoked more than 100 cigarettes in your lifetime?

a) Yes
b) No
c) Don't know

Display this Question:

If Have you/ has the mother smoked more than 100 cigarettes in your lifetime? = Yes

55. How many cigarettes a day did you / the mother usually smoke during the following time periods?

One pack is usually 20 cigarettes.

56. What about e-cigarettes (like vaping) or other tobacco products like a cigar or hookah?

57. During what time periods did you / the mother smoke, vape or use other tobacco products?

	How many cigarettes did you smoke in the [read time period]?	How many of times a day did you vape/use e-Cigs or other types of Tobacco?
	Number of Cigarettes/Day	Number of E-Cigs or Vape or Tobacco/Day
12 months prior to pregnancy		
1st trimester of pregnancy		
2nd trimester of pregnancy		
3rd trimester of pregnancy		
0-24 months after ${q://QID987/ChoiceTextEntryValue/1}'s birth		
After 24 months of ${q://QID987/ChoiceTextEntryValue/1}'s birth until the reference date		

Family Cancer History

Now I would like to ask you some questions about your family's medical history. Please take your time and focus on the blood relatives of the child. Please try to recall whether any of the relatives were ever diagnosed with cancer. Leukemia, brain tumors, lymphomas, and Hodgkin's disease are all types of cancer and should be included.

58. Please record any relatives that have had cancer, and what kinds of cancer they had?

	*Any information about the cancer type, site, etc. should be entered here			If answer yes to cancer
	Yes	No	Don't know	Cancer Type
Mother	○	○	○	
Father	○	○	○	
Maternal Grandmother	○	○	○	
Maternal Grandfather	○	○	○	
Paternal Grandmother	○	○	○	
Paternal Grandfather	○	○	○	
Siblings of CHILD (1)	○	○	○	
Siblings of CHILD (2)	○	○	○	
Siblings of CHILD (3)	○	○	○	

59. During pregnancy, did you/ the mother ever have any of the following medical procedures?

During pregnancy, did you/ the mother ever have any of the following medical procedures?

	Column Options			Column Options					Column Options
	Receive this procedure?			During what time period?					Frequency
	Yes	No	Don't know	1 yr prior to conception	Pregnancy 1st Trimester	Pregnancy 2nd Trimester	Pregnancy 3rd Trimester	Don't know	How many times did this happen?
Diagnostic X-rays	○	○	○	☐	☐	☐	☐	☐	
Radiation therapy	○	○	○	☐	☐	☐	☐	☐	
Dental X-rays - Traditional	○	○	○	☐	☐	☐	☐	☐	
Dental X-rays - Panoramic	○	○	○	☐	☐	☐	☐	☐	

60. Did the child ever have any of the following procedures, prior to their first cancer diagnosis?

	Did your child ever receive this procedure?			If yes, what was the reason?	Frequency of Procedure	Age
	Y	N	Don't know	Age	Frequency of Procedure	Age
Diagnostic X-rays	○	○	○			
Radiation therapy	○	○	○			
Dental X-rays - Traditional	○	○	○			
Dental X-rays - Panoramic	○	○	○			

The following questions focus on your child's medical history before their first cancer diagnosis.

61. Did the child ever have any of the following infections?

	${q://QID987/ChoiceTextEntryValue/1}'s Infections			Age at diagnosis
	Y	N	Don't know	Age at diagnosis
Measles	○	○	○	
Chickenpox	○	○	○	
Shingles	○	○	○	
Cytomegalovirus	○	○	○	
Hepatitis	○	○	○	
Monocleosis	○	○	○	
Herpes virus	○	○	○	

62. At the time the child was born, what was your estimated total household income before taxes?

Please include income such as Medicaid, Social Security, and Unemployment payments.

a) Less than 10 Thousand Dollars per year
b) 10 to 30 Thousand Dollars
c) 30 to 50 Thousand Dollars
d) 50 to 70 Thousand Dollars
e) 70 to 90 Thousand Dollars
f) 90 to 110 Thousand Dollars
g) More than 110 Thousand Dollars
h) Don't know

63. Is there anything else you would like to share with the research team regarding your residence, occupation, exposures, or anything else addressed in this questionnaire that you feel is relevant to this study?

Please describe here: ____

Thank you for completing this questionnaire. Now that you have completed the survey, the research team will be mailing your $25 payment card to the address you provided on your postcard.

We send out the payment cards every Thursday, so you can likely expect to receive it within two weeks of this date. If you don't receive it within 2 weeks, please call the project office at 412-648-5185, and we can investigate.

Upon receipt, you will need to call a project staff member to activate your card. These instructions will be included with the card mailing.

Thank you again for your participation in this research study. Your information could be used to further other studies in this area.

1. Would you be willing to participate in follow-up studies or to give us additional information after the survey has concluded? (not including studies with specimen collections - like blood, saliva, etc.)

a) Yes
b) No
c) Don't know

2. Would you be willing to participate in follow-up studies to give us biosamples after the survey has concluded? Some examples of these may include blood sample, buccal swabs, other specimens.

a) Yes
b) No
c) Don't know

Supplementary Tables

Supplementary Table S1. Distribution of Cases by Fine Categories of Childhood Malignancies in Southwestern PA 2010-2019)

Class (most detailed)	**Frequency**	**Percent**
(a.1) Precursor cell leukemias	112	22.1
(a.2) Mature B-cell leukemias	2	.4
(b) Acute myeloid leukemias	30	5.9
(c) Chronic myeloproliferative diseases	14	2.8
(d) Myelodysplastic syndrome and other myeloproliferative diseases	5	1.0
(e) Unspecified and other specified leukemias	2	.4
(a) Hodgkin lymphomas	52	10.3
(b.1) Precursor cell lymphomas	5	1.0
(b.2) Mature B-cell lymphomas (except Burkitt lymphoma)	12	2.4
(b.3) Mature T-cell and NK-cell lymphomas	5	1.0
(c) Burkitt lymphoma	5	1.0
(d) Miscellaneous lymphoreticular neoplasms	25	4.9
(e) Unspecified lymphomas	1	.2
(a.1) Ependymomas	9	1.8
(a.2) Choroid plexus tumor	5	1.0
(b) Astrocytomas	87	17.2
(c.1) Medulloblastomas	13	2.6
(c.2) PNET	1	.2
(d.1) Oligodendrogliomas	3	.6
(d.2) Mixed and unspecified gliomas	31	6.1
(e.1) Pituitary adenomas and carcinomas	12	2.4
(e.2) Tumors of the sellar region (craniopharyngiomas)	7	1.4
(e.3) Pineal parenchymal tumors	1	.2
(e.4) Neuronal and mixed neuronal-glial tumors	20	3.9
(e.5) Meningiomas	3	.6
(f) Unspecified intracranial and intraspinal neoplasms	2	.4
(a) Osteosarcomas	18	3.6
(b) Chondrosarcomas	2	.4
(c.1) Ewing tumor and Askin tumor of bone	20	3.9
(d.2) Malignant chordomas	2	.4
(d.4) Miscellaneous malignant bone tumors	1	.2

Supplementary Table S2. Distributions of UNGD Activities Metric Within 5 Miles of Buffer Zone among Children with Any of the Four Malignancies and their County-Matched Controls by Different Time Periods of Exposure in the Birth Record-Based Analysis (n=498)

Exposure Metrics within 5 miles*	Group	Time period†	Exposed N‡	Mean	Std Dev	Minimum	Maximum	10th Pctl	25th Pctl	Median	75th Pctl	90th Pctl
Overall UNGD activities	Cases	Pregnancy (T1)	94	3.50E-5	5.8E-5	6.06E-7	4.22E-4	4.71E-6	6.31E-6	12.0E-6	3.30E-5	10.9E-5
		Postnatal (T2)	311	30.2E-5	74.3E-5	7.21E-7	79.5E-4	8.91E-6	24.0E-6	82.0E-6	21.7E-5	65.0E-5
	County-Matched Controls	Pregnancy (T1)	99	3.70E-5	8.40E-5	1.43E-7	7.60E-4	2.73E-6	5.42E-6	10.0E-6	4.5E-5	7.80E-5
		Postnatal (T2)	297	24.3E-5	67.1E-5	8.99E-7	71.6E-4	10.0E-6	28.0E-6	61.0E-6	20.2E-5	54.5E-5
Well pad construction (counts/m²)	Cases	Pregnancy (T1)	48	4.54E-6	5.90E-6	4.32E-7	2.40E-5	6.04E-7	7.91E-7	2.03E-6	5.74E-6	1.60E-5
		Postnatal (T2)	287	39.0E-6	105.0E-6	4.70E-7	125.0E-5	7.71E-7	23.1E-7	7.54E-6	28.0E-6	9.30E-5
	County-Matched Controls	Pregnancy (T1)	50	9.06E-6	22.0E-6	1.28E-7	12.8E-5	5.59E-7	7.50E-7	1.87E-6	6.57E-6	1.8E-5
		Postnatal (T2)	272	26.0E-6	55.0E-6	0.61E-7	43.6E-5	6.41E-7	16.4E-7	6.18E-6	22.0E-6	6.2E-5
Drilling (counts/m²)	Cases	Pregnancy (T1)	60	3.20E-5	5.00E-5	3.36E-8	2.88E-4	8.96E-7	2.81E-6	8.86E-6	4.50E-5	10.0E-5
		Postnatal (T2)	295	22.7E-5	64.1E-5	10.21E-8	74.8E-4	23.3E-7	9.49E-6	49.0E-6	16.2E-5	47.6E-5
	County-Matched Controls	Pregnancy (T1)	62	3.40E-5	7.00E-5	7.69E-8	5.02E-4	3.61E-7	1.58E-6	13.0E-6	3.90E-5	7.00E-5
		Postnatal (T2)	280	18.1E-5	58.7E-5	12.98E-8	65.0E-4	18.5E-7	9.37E-6	37.0E-6	12.5E-5	43.3E-5
Hydraulic fracturing (depth in m/m²)	Cases	Pregnancy (T1)	60	0.019	0.060	3.60E-5	0.445	1.83E-4	7.59E-4	3.82E-3	0.012	0.031
		Postnatal (T2)	283	0.084	0.202	4.90E-5	1.331	9.51E-4	30.9E-4	16.1E-3	0.059	0.197
	County-Matched Controls	Pregnancy (T1)	60	0.016	0.042	6.40E-5	0.309	1.31E-4	9.28E-4	3.57E-3	0.018	0.033
		Postnatal (T2)	268	0.077	0.249	7.00E-5	3.150	9.46E-4	42.2E-4	15.3E-3	0.052	0.201
Production (volume in m³/m²)	Cases	Pregnancy (T1)	88	0.787	4.64	20.0E-5	43.12	2.35E-3	0.013	0.075	0.316	0.813
		Postnatal (T2)	279	2.741	14.85	6.70E-5	190.9	6.93E-3	0.048	0.348	1.347	3.540
	County-Matched Controls	Pregnancy (T1)	88	0.302	0.857	5.58E-6	7.40	1.46E-3	0.011	0.046	0.321	0.725
		Postnatal (T2)	269	2.145	12.30	1.43E-6	154.8	9.59E-3	0.072	0.445	1.225	2.621
Summed Z score§	Cases	Pregnancy (T1)	94	2.251	4.518	-0.476	33.49	-0.075	0.082	0.681	2.249	6.944
		Postnatal (T2)	311	0.817	3.806	-1.001	25.90	-0.942	-0.819	-0.481	0.656	3.091
	County-Matched Controls	Pregnancy (T1)	99	2.569	7.219	-0.565	64.86	-0.270	0.004	0.366	2.920	5.274
		Postnatal (T2)	297	0.463	3.368	-0.999	29.02	-0.923	-0.807	-0.560	0.238	2.178
Well counts	Cases	Pregnancy (T1)	97	27.48	35.82	1.00	154.00	1.00	4.00	9.00	34.00	85.00
		Postnatal (T2)	306	39.26	46.82	1.00	296.00	2.00	7.00	21.50	59.00	103.00
	County-Matched Controls	Pregnancy (T1)	99	22.31	29.05	1.00	117.00	1.00	2.00	10.00	28.00	67.00
		Postnatal (T2)	293	37.97	47.26	1.00	333.00	2.00	6.00	18.00	58.00	101.00
IDW well counts (counts/m²)	Cases	Pregnancy (T1)	97	1.44E-6	2.44E-6	1.68E-8	1.40E-5	4.49E-8	1.08E-7	3.26E-7	1.86E-6	3.98E-6
		Postnatal (T2)	306	3.09E-6	5.74E-6	1.56E-8	4.30E-5	6.40E-8	2.02E-7	8.94E-7	3.38E-6	7.84E-6
	County-Matched Controls	Pregnancy (T1)	99	1.31E-6	2.37E-6	1.56E-8	1.40E-5	2.44E-8	6.76E-8	3.55E-7	1.23E-6	4.29E-6
		Postnatal (T2)	293	2.47E-6	4.70E-6	1.65E-8	4.40E-5	5.04E-8	18.45E-8	6.48E-7	2.81E-6	6.68E-6

* See the formulas for calculation of all metrics in Table 14a.

† The pregnancy period was defined from the conception to birth using the gestation age on the birth records whereas the postnatal period from birth to the index date, which was the date of cancer diagnosis for cases and the corresponding date for the matched controls.

‡ The difference between total N and Exposed N was the number of subjects with non-exposure (not shown).

§ calculated as $\sum_{ij}^{k} \frac{x_{ij}-\mu_{.j}}{\sigma_{.j}}$; where i is for subject; j, specific phases of UNGD activities (=k); x, individual measurement of UNGD activity; μ, mean; and σ, standard deviation.

Supplementary Table S3. Distributions of Sociodemographic Characteristics of Childhood Cancer Cases Using Birth Record Information: 213 County-Matched Case-Control pairs

Sociodemographic Characteristic	Cases (N=213)		County-Matched Controls (N=213)	
	Frequency	*Percent*	*Frequency*	*Percent*
Sex at Birth				
Female	99	46.5	99	46.5
Male	114	53.5	114	53.5
Maternal Age (years)				
<20	7	3.3	7	3.3
20-24	25	11.7	24	11.3
25-29	54	25.4	60	28.2
30-34	74	34.7	81	38.0
≥35	53	24.9	41	19.2
Maternal Race				
White	209	98.1	209	98.1
Black	2	0.9	2	0.9
Other	2	0.9	2	0.9
Maternal Education				
≤ 8th Grade	0	0.0	1	0.5
Some High School	10	4.7	10	4.7
High School Diploma	50	23.5	30	14.1
Some College	43	20.2	45	21.1
College Degree or Higher	108	50.7	127	59.6
Unknown	2	0.9	0	0.0
Number of Prenatal Visits				
0-7	13	6.1	16	7.5
8-12	106	49.8	111	52.1
13-16	77	36.1	77	36.1
≥17	10	4.7	5	2.4
Unknown	7	3.3	4	1.9
Birth weight				
≤2500 g	12	5.6	10	4.7
2501- 4000 g	173	81.2	180	84.5
>4000 g	28	13.2	22	10.3
Unknown	0	0.0	1	0.5
Smoking during pregnancy				
Never	184	86.4	192	90.1
Ever	25	11.7	20	9.4
Unknown	4	1.9	1	0.5
Gestation in weeks				
Mean (S.D.)	38.9(1.66)		38.7(2.02)	

Supplementary Table S4. Descriptives of Residential History Characteristics for Cases and County-Matched Controls

Variable	Cases (N=213) *		County Matched Controls (N=213) **	
	Frequency	*Percent*	*Frequency*	*Percent*
Pre-1970s Housing				
Ever	71	58.2	102	62.6
Never	51	41.8	61	37.4
Missing/dk	27		8	
Item not presented	64		42	
Residence Exterminated				
Ever	19	15.2	26	17.8
Never	106	84.8	120	82.2
Missing/dk	24		25	
Item not presented	64		42	
Pesticide/Herbicide Used in Yard				
Ever	54	45.0	82	55.4
Never	66	55.0	66	44.6
Missing/dk	29		23	
Item not presented	64		42	
Water Tested				
Ever	26	23.4	29	27.6
Never	85	76.6	76	72.4
Missing/dk	38		46	
Item not presented	64		42	
Radon Tested				
Ever	66	58.4	75	63.0
Never	47	41.6	44	37.0
Missing/dk	36		52	
Item not presented	64		42	
Radon Remediation				
Ever	26	22.2	25	19.5
Never	91	77.8	103	80.5
Missing/dk	32		43	
Item not presented	64		42	

*Out of 213 cases, a total of 149 cases had the opportunity to respond to surveys with a complete survey/residential history, 64 additional participants answered the short residential questionnaire without these items

**Out of 213 county-matched controls, a total of 171 county-matched controls had the opportunity to respond to surveys with a complete residential history, 42 filled out the short residential questionnaire without these items

Supplementary Table S4 Continued. Residential History Characteristics for Cases and County-Matched Controls

Variable	Cases (N=213) *		County-matched Controls (N=213) **	
	Frequency	*Percent*	*Frequency*	*Percent*
Attached Garage				
Ever	80	62.5	85	49.7
Never	48	37.5	86	50.3
Missing/dk	21		0	
Item not presented	64		42	
Well Water at Home				
Ever	20	14.8	18	10.4
Never	109	85.2	155	89.6
Missing/dk	20			
Item not presented	64		42	
[1]Perception – Residence within 1 mile of Industrial Facility				
Ever	36	25.0	46	30.1
Never	108	75.0	107	69.9
Missing/dk	5		18	
[1]Perception – Residence within 1 mile of Farm				
Ever	40	27.6	37	25.9
Never	105	72.4	106	74.1
Missing/dk	4		28	
[1]Perception – Residence within 1 mile of Oil and Gas Industry				
Ever	23	17.4	23	18.1
Never	109	82.6	104	81.9
Missing/dk	15		44	

*Out of 213 cases, a total of 149 cases had the opportunity to respond to surveys with a complete survey/residential history, 64 additional participants answered the short residential questionnaire only

**Out of 213 county-matched controls, a total of 171 county-matched controls had the opportunity to respond to surveys with a complete residential history, 42 filled out the short residential questionnaire only

1 item presented to all 213 cases and control survey respondents

Supplementary Table S5. Total overall unconventional natural gas drilling (UNGD) activities and risk of four childhood/adolescent 4 malignances combined during two exposure periods in Southwestern Pennsylvania 2010-2019

Overall UNGD activities by exposure period	**Survey-based Study with County-matched Controls (213 case-control pairs)**			**Birth Record-based Study with County-matched Controls (498 case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**	***Controls***	***Cases***	**OR (95% CI)†**
T1: During Mother's Pregnancy						
Non-exposed	172	174	1.00	399	404	1.00
Exposed*	41	39	0.76 (0.30-1.89)	99	94	0.82 (0.47-1.41)
By buffer zone						
Non-exposed	172	174	1.00	399	404	1.00
(2-5] miles	26	30	0.80 (0.32-2.03)	64	63	0.84 (0.48-1.46)
(1-2] miles	6	6	0.46 (0.08-2.47)	24	22	0.72 (0.31-1.67)
(0.5-1] miles	9	3	0.16 (0.02-1.08)	9	7	0.65 (0.19-2.26)
[0-0.5] miles				2	2	0.81 (0.05-14.62)
P trend‡			*0.0643*			*0.3817*
By overall UNGD activities within 5 miles						
Non-exposed	172	174	1.00	399	404	1.00
Lowest (1st) quartile	10	14	1.17 (0.37-3.68)	24	17	0.63 (0.29-1.34)
Low-middle (2nd) quartile	10	8	0.51 (0.11-2.36)	25	22	0.77 (0.37-1.64)
High-middle (3rd) quartile	10	12	0.72 (0.20-2.58)	25	36	1.40 (0.63-3.14)
Highest (4th) quartile	11	5	0.26 (0.05-1.29)	25	19	0.75 (0.31-1.83)
P trend‡			*0.1443*			*0.7587*

* Exposed were individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls); non-exposed otherwise.

† All odds ratios (ORs) and their 95% confidence intervals (CIs) for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and following variables including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and superfund site (no, yes).

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

Supplementary Table S5 Continued. Total overall unconventional natural gas drilling (UNGD) activities and risk of four childhood/adolescent 4 malignances combined during two exposure periods in Southwestern Pennsylvania 2010-2019

Overall UNGD activities by exposure period	**Survey-based Study with County-matched Controls (213 case-control pairs)**			**Birth Record-based Study with County-matched Controls (498 case-control pairs)**		
	Controls	***Cases***	**OR (95% CI)†**	***Controls***	***Cases***	**OR (95% CI)†**
T2: From Birth to Index Date§						
Non-exposed	84	74	1.00	201	187	1.00
Exposed*	129	139	1.48 (0.88-2.5)	297	311	1.24 (0.87-1.78)
By buffer zone						
Non-exposed	84	74	1.00	201	187	1.00
(2-5] miles	72	75	1.43 (0.83-2.46)	178	170	1.18 (0.82-1.71)
(1-2] miles	24	38	2.09 (0.97-4.49)	72	77	1.49 (0.89-2.51)
(0.5-1] miles	21	14	0.82 (0.32-2.11)	37	38	1.61 (0.85-3.03)
[0-0.5] miles	12	12	1.47 (0.56-3.86)	10	26	**3.94 (1.66-9.39)**
P trend‡			*0.6289*			***0.0041***
By overall UNGD activities within 5 miles						
Non-exposed	84	74	1.00	201	187	1.00
Lowest (1st) quartile	32	48	**2.24 (1.14-4.41)**	74	86	1.40 (0.91-2.14)
Low-middle (2nd) quartile	32	16	0.70 (0.33-1.49)	74	50	0.76 (0.46-1.25)
High-middle (3rd) quartile	32	39	1.55 (0.79-3.04)	74	88	**1.69 (1.01-2.82)**
Highest (4th) quartile	33	36	1.40 (0.61-3.21)	75	87	1.79 (1.00-3.19)
P trend‡			*0.4496*			*0.0975*
By overall UNGD activities within 2 miles**						
Non-exposed	84	74	1.00	201	187	1.00
Lowest (1st) quartile	14	17	1.84 (0.74-4.61)	29	37	1.74 (0.93-3.27)
Low-middle (2nd) quartile	14	23	2.07 (0.84-5.08)	30	32	1.48 (0.77-2.84)
High-middle (3rd) quartile	14	9	0.72 (0.25-2.11)	30	30	1.41 (0.72-2.77)
Highest (4th) quartile	15	15	1.87 (0.66-5.3)	30	42	**2.16 (1.10-4.25)**
P trend‡			*0.4837*			***0.0321***

* Exposed were individuals who lived within 5 miles of any UNGD activity during mother's pregnancy (T1) or from birth to the index date (i.e., date of cancer diagnosis for cases or the same date for matched controls); non-exposed otherwise.

† All odds ratios (ORs) and their 95% confidence intervals (CIs) for different buffer zones or levels of exposures against non-exposed group were derived from unconditional logistic regression models with adjustment for matching factors (age, sex, race, and county of residence) and following variables including maternal age at childbirth (years), maternal education level, maternal smoking status at childbirth (no, yes), gestation age (weeks), birthweight (g), toxics release inventory (TRI) (no, yes), uranium mill tailings remedial action sites {UMTRA} (no, yes), and superfund site (no, yes).

‡ The same unconditional logistic models were used for linear trend test for the exposure variable in ordinal values (1, 2 for high or low) that also included non-exposed individuals (coded as 0) to maintain the case-control matched pairs.

§ The index date was the date of malignancy diagnosis for cases and the same corresponding date for matched controls.

** The same data for those with UNGD exposure within 2-5 mile of buffer zone were included in this modelling but not presented repeatedly.