



The association between natural gas well activity and specific congenital anomalies in Oklahoma, 1997–2009

Amanda E. Janitz*, Hanh Dung Dao, Janis E. Campbell, Julie A. Stoner, Jennifer D. Peck

Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

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ABSTRACT

Background: Natural gas drilling may pose multiple health risks, including congenital anomalies, through air pollutant emissions and contaminated water. Two recent studies have evaluated the relationship between natural gas activity and congenital anomalies, with both observing a positive relationship.

Objectives: We aimed to evaluate whether residence near natural gas wells is associated with critical congenital heart defects (CCHD), neural tube defects (NTD), and oral clefts in Oklahoma, the third highest natural gas producing state in the US.

Methods: We conducted a retrospective cohort study among singleton births in Oklahoma ($n = 476,600$) to evaluate natural gas activity and congenital anomalies. We calculated an inverse distance-squared weighted (IDW) score based on the number of actively producing wells within a two-mile radius of the maternal residence during the month of delivery. We used modified Poisson regression with robust error variance to estimate prevalence proportion ratios (PPR) and 95% confidence intervals (CI) for the association between tertiles of natural gas activity (compared to no wells) and CCHD, NTD, and oral clefts adjusted for maternal education.

Results: We observed an increased, though imprecise, prevalence of NTDs among children with natural gas activity compared to children with no wells (2nd tertile PPR: 1.34, 95% CI: 0.93, 1.93; 3rd tertile PPR: 1.20, 95% CI: 0.82, 1.75). We observed no association with CCHD or oral clefts overall. Specific CCHDs of common truncus, transposition of the great arteries, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, interrupted aortic arch, and total anomalous pulmonary venous connection were increased among those living in areas with natural gas activity compared to those living in areas without activity, though not statistically significant.

Discussion: Our results were similar to previous studies for NTDs and specific CCHDs. Future directions include evaluating the association between specific phases of the drilling process and congenital anomalies to better refine the relevant exposure period.

1. Introduction

Natural gas drilling may pose multiple health risks, including congenital anomalies, through air pollutant emissions and contaminated water (Adgate et al., 2014; Esswein et al., 2014; McKenzie et al., 2012; Webb et al., 2014). Through the various phases of natural gas drilling, including increased diesel traffic, use of generators, and the processes of drilling, hydraulic fracturing, and production, several categories of pollutants are emitted into the environment. These chemical hazards include particulate matter, polycyclic aromatic hydrocarbons (PAH), endocrine disrupting chemicals, heavy metals (including arsenic and

manganese), and several air toxics (benzene, toluene, ethylbenzene, and xylene [BTEX]) among others, with physical, safety, and water scarcity hazards potentially associated with various health outcomes (Allshouse et al., 2017; Webb et al., 2017). Two recent studies have specifically evaluated the relationship between natural gas activity and congenital anomalies, with both observing a positive relationship (Ma et al., 2016; McKenzie et al., 2014). While McKenzie et al. (2014) worked with the Colorado Responds to Children with Special Needs registry, Ma et al. (2016) were limited by use of an ecologic design and birth certificates as the source of children with anomalies, which could underestimate the prevalence compared to a birth defects registry

Abbreviations: BTEX, benzene, toluene, ethylbenzene, and xylene; CCHD, Critical congenital heart defects; CI, Confidence interval; IDW, Inverse distance-squared weighted; NTD, Neural tube defects; OBDR, Oklahoma Birth Defects Registry; PAH, polycyclic aromatic hydrocarbons; PPR, Prevalence proportion ratio; DAG, directed acyclic graph; SES, socioeconomic status

* Corresponding author at: 801 NE 13th St., CHB 309, Oklahoma City, OK 73104, USA.

E-mail address: amanda-janitz@ouhsc.edu (A.E. Janitz).

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(Boulet et al., 2011; Zollinger et al., 2006).

The biologic mechanism by which emissions from natural gas drilling and production may cause congenital anomalies is unclear. However, studies have focused on the biologic mechanisms for chemicals emitted through oil and gas production to cause low birth weight, intrauterine growth restriction, and prematurity in infants (Kannan et al., 2006; Slama et al., 2008). In addition, several studies have reported adverse reproductive health outcomes among mouse offspring that ingested contaminated water with known endocrine disrupting chemicals produced during oil and gas drilling activities (Boule et al., 2018; Kassotis et al., 2015; Kassotis et al., 2016).

A potential biologic mechanism that appears to be more closely related to congenital anomalies is oxidative stress, leading to DNA damage and increasing the number of placental DNA adducts (Kampa and Castanas, 2008; Kannan et al., 2006; Slama et al., 2008). Perera et al. (1999) reported that fetal tissue may be slower to metabolize toxic substances with evidence of DNA adducts from PAH in rodent fetal tissue, though levels of PAH were only one-tenth of those in the mother. Ren et al. (2011) observed a positive association between PAH measured in maternal placentas and neural tube defects (NTD) among their children after adjustment for maternal and child characteristics including folic acid supplementation (Odds Ratio [OR]: 6.0, 95% confidence interval [CI]: 2.0, 18.5). Benzene is known to cross the placenta, with levels in cord blood being equal to or greater than levels in the mother (Agency for Toxic Substances and Disease Registry, 2007). Benzene has also been associated with NTDs in recent studies (Brender et al., 2002; Lupo et al., 2011; Swartz et al., 2015), though results are mixed (Janitz et al., 2018; Tanner et al., 2015). The nervous system may be more sensitive to the effects of air pollutants than other body systems due to the lack of blood brain barrier until after birth (Perera et al., 1999). Evidence for other types of congenital anomalies is lacking, but may follow similar pathways described for other birth outcomes (Webb et al., 2014; Webb et al., 2017).

In Oklahoma, the number of new oil or gas well completions increased from approximately 3000 wells in 2000 to 4700 wells in 2008, with a subsequent decrease in 2009 to approximately 2500 wells (Murray, 2013). The majority of these wells were vertically drilled, with horizontal drilling increasing over time, accounting for approximately 20% of wells in 2009. The authors also estimated that 44% of horizontally drilled wells used hydraulic fracturing based on reports to the Oklahoma Corporation Commission.

We aimed to evaluate whether residence near natural gas wells is associated with critical congenital heart defects (CCHD), NTDs, and oral clefts in Oklahoma, the third highest natural gas producing state in the US (U.S. Energy Information Administration, 2017). Our study adds to the limited literature by conducting multiple sensitivity analyses, including evaluating natural gas well activity during the estimated month of conception and inclusion of ZIP centroid-level geocodes, which have not been previously analyzed.

2. Methods

2.1. Study design, data sources, and outcomes

We conducted a retrospective cohort study of live births in Oklahoma from January 1, 1997 through December 31, 2009 using data from the Oklahoma State Department of Health (Fig. 1). Data on children with congenital anomalies were obtained from the Oklahoma Birth Defects Registry (OBDR), which is an active surveillance system that collects information on all congenital anomalies identified by birthing hospitals in Oklahoma. Congenital anomalies can be reported up to age 6 years (for the included birth years), but signs/symptoms of the anomaly must be present by age 2 years (Oklahoma State Department of Health, 2018). We linked the records of children with congenital anomalies to birth certificates using Registry Plus™ Link Plus software v. 2.0 (CDC, Atlanta, GA), with 95% of records in OBDR

linking to a birth certificate resulting in 26,023 children with anomalies and 629,430 children without anomalies. We obtained information on demographic and birth characteristics from the birth certificate for all children. We geocoded maternal residence at delivery from the birth certificate masked to congenital anomaly status using the Texas A&M Geocoding Service toolbox in ArcGIS v. 10.4 (Texas A&M University, 2016) and using 2014 TIGER/Line files (U.S. Census Bureau, 2017).

We excluded any children whose residence was outside of Oklahoma or not geocodable (N = 7606), plural births (N = 17,932), and non-CCHD, NTDs, and oral clefts (N = 22,225). Due to Tribal sovereignty, the Oklahoma Corporation Commission does not have jurisdiction over oil and gas production in the Osage Nation Reservation. Thus, we excluded children residing in Osage County in northeastern Oklahoma due to the lack of available oil and gas production records for this region (N = 5595). Furthermore, we excluded children whose residences geocoded to a ZIP code centroid (N = 125,495), though these children were included in a sensitivity analysis to evaluate potential selection bias. Of those who geocoded to the ZIP code centroid, 42% were Post Office Boxes (N = 53,210), 34% were rural routes (N = 43,163), 22% were street addresses that were unable to be geocoded to the street level (N = 28,144), and 0.8% had incomplete addresses with only a ZIP code available (N = 978).

We included CCHDs, NTDs (spina bifida and anencephaly), and oral clefts (cleft lip and cleft palate) in our analysis (Table S1) (N = 1665 children). CCHDs are conditions that are often life-threatening within the first few weeks of life and are more validly reported to OBDR than other types of congenital heart defects (Mahle et al., 2009; Olney et al., 2015; Tanner et al., 2015). CCHDs include the following defects: common truncus/truncus arteriosus, transposition of the great arteries, double outlet right ventricle, Tetralogy of Fallot, single ventricle, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, Ebstein anomaly, hypoplastic left heart syndrome, coarctation of aorta, interrupted aortic arch, and total anomalous pulmonary venous connection.

2.2. Natural gas well data

We obtained historical data on producing natural gas wells from the Oklahoma Corporation Commission for each year of the study. These data contained information on the latitude and longitude of the well and monthly production levels of natural gas. However, we did not have information on whether the well was horizontally drilled or if hydraulic fracturing was used. We used the production levels to determine whether a natural gas well was actively producing and classified a well as active if natural gas production was reported during at least one month in a given year. We used an inverse distance-squared weighting (IDW) method to calculate the density of actively producing wells during the month of birth within a 2-, 5-, and 10-mile radius of the maternal residence at delivery using the following formula:

$$IDW_a = \sum_{i=1}^n \frac{1}{d_i^2}$$

where a = buffer distance (2-, 5-, 10-miles from birth residence), i = each well within the buffer, n = total number of wells within the buffer, and d = distance from birth residence to any actively producing natural gas well within the buffer. This method allows for assignment of a higher score to wells that were closer to the residence and a smaller score to wells that are farther away. Whitworth et al. (2018) and Whitworth et al. (2017) used this formula to calculate IDW at 0.5-, 2-, and 10-mile buffers, whereas McKenzie et al. (2014) and Stacy et al. (2015) used an IDW method without squaring the distance for all wells within the specified buffer (2-, 5-, and 10-mile buffers in McKenzie et al. (2014) and 10-mile buffer in Stacy et al. (2015)). Using the squared distance allowed for higher IDW for wells close to the residence and lower IDW for wells further from the residence than would be

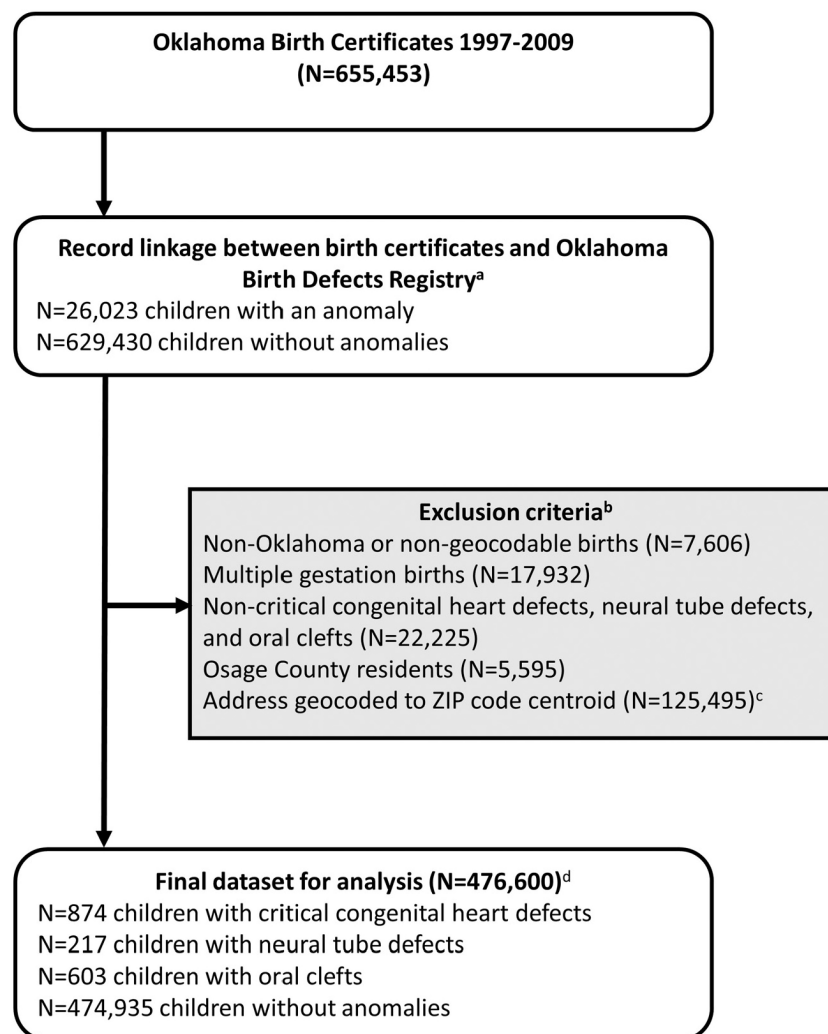


Fig. 1. Flow diagram describing study design and exclusion criteria. Footnotes: ^a95% of children in the Oklahoma Birth Defects Registry linked with a birth certificate. All birth records without a linked congenital anomaly record were classified as non-congenital anomalies. ^bExclusion criteria listed in order of exclusion. ^cWe conducted sensitivity analysis including zip-code level geocodes. ^d29 children have more than one included congenital anomaly.

calculated using the base (not squared) distance. Although we planned to additionally evaluate a 0.5-mile buffer around the birth residence based on previous studies indicating potential health hazards at this distance (McKenzie et al., 2012; Whitworth et al., 2017; Whitworth et al., 2018), the number of children with the included anomalies was too small for analysis at buffers < 2 miles. Thus, our primary analysis used the 2-mile buffer, with sensitivity analyses evaluating 5- and 10-mile buffers.

The IDW summed well counts at the 2-mile buffer was classified into tertiles (1st: 0.25–1.88, 2nd: > 1.88–9.00, 3rd: > 9.00–47,679.13) for comparison to those with no recorded wells within the buffer as the reference category. To evaluate specific CCHDs, NTDs, and oral clefts, we created a dichotomous variable to compare children with a birth residence near any actively producing natural gas well to those with no wells within a 2-mile buffer of the birth residence.

2.3. Statistical analysis

We used modified Poisson regression with robust error variance to calculate prevalence proportion ratios (PPR) and 95% confidence intervals (CI) for children with CCHD (N = 874), NTDs (N = 217), and oral clefts (N = 603) using complete case analysis (29 of these children have more than one of the included anomalies). Children without any anomaly (N = 474,935) were included as a comparison group for all

three congenital anomaly categories. We used a directed acyclic graph (DAG) to determine the minimally sufficient set of confounding factors based on the literature (Fig. S1, Table S2) (Casey et al., 2016; Ma et al., 2016; McKenzie et al., 2014; Stacy et al., 2015; Whitworth et al., 2017; Whitworth et al., 2018), which considered birth certificate variables of year of birth, sex, race/ethnicity (non-Hispanic [NH] white, NH African American, NH American Indian/Alaska Native, NH Asian/Pacific Islander, and Hispanic as reported by the mother), gestational age at delivery in weeks, birth weight in grams, urban/rural status of census block at delivery (based on the 2000 US Census), maternal factors of age at delivery in years, marital status (married/not married), prenatal care (yes/no), parity (number of previous live births), tobacco use during pregnancy (yes/no), and education (less than high school, completed high school, or more than high school) (as a surrogate for socioeconomic status [SES]). Our DAG analysis using DAGitty (Textor et al., 2011; Textor, 2016) indicated we should control for either urbanization or maternal education (not both variables) in our multivariable model. It is unclear from the literature whether urbanization is a surrogate for natural gas exposure or SES, thus we chose to adjust our multivariable models for maternal education only (Tselios, 2013).

We conducted the following sensitivity analyses: 1) evaluation of a fully adjusted model including all potential covariates noted above; 2) using buffers of 5- and 10-miles around the birth residence; 3) calculating the IDW using the base distance (not squared) for more direct

Table 1
Distribution of birth characteristics by congenital anomaly status, Oklahoma singleton births, 1997–2009.

	Critical congenital heart defects (N = 874)	Neural tube defects (N = 217)	Oral clefts (N = 603)	No congenital anomaly (N = 474,935)
	N (%)	N (%)	N (%)	N (%)
Sex				
Female	369 (42.2)	106 (48.8)	236 (39.1)	232,881 (49.0)
Male	505 (57.8)	111 (51.2)	367 (60.9)	242,046 (51.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.0)
Race/ethnicity				
Non-Hispanic White	576 (65.9)	147 (67.7)	419 (69.5)	310,128 (65.3)
Non-Hispanic African American	76 (8.7)	18 (8.3)	37 (6.1)	50,986 (10.7)
Non-Hispanic American Indian	84 (9.6)	14 (6.5)	60 (10.0)	41,250 (8.7)
Non-Hispanic Asian/unknown ^a	29 (3.3)	< 6 ^b (1.8)	20 (3.3)	14,044 (3.0)
Hispanic	109 (12.5)	34 (15.7)	67 (11.1)	58,527 (12.3)
Maternal age at delivery (years)				
< 20	107 (12.2)	27 (12.4)	94 (15.6)	67,499 (14.2)
20–34	671 (76.8)	170 (78.3)	459 (76.1)	367,703 (77.4)
≥ 35/unknown ^a	96 (11.0)	20 (9.2)	50 (8.3)	39,733 (8.4)
Parity (number of previous live births)				
0	358 (41.0)	87 (40.1)	220 (36.5)	193,220 (40.7)
1	255 (29.2)	66 (30.4)	193 (32.0)	149,229 (31.4)
2	162 (18.5)	37 (17.1)	110 (18.2)	81,456 (17.2)
≥ 3	99 (11.3)	27 (12.4)	80 (13.3)	50,997 (10.7)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	33 (0.0)
Gestational age at delivery (weeks)				
< 37	153 (17.5)	66 (30.4)	82 (13.6)	37,846 (8.0)
37–39	494 (56.5)	119 (54.8)	343 (56.9)	261,327 (55.0)
≥ 40	194 (22.2)	25 (11.5)	152 (25.2)	161,879 (34.1)
Unknown	33 (3.8)	7 (3.2)	26 (4.3)	13,883 (2.9)
Birth weight (grams)				
< 1500	20 (2.3)	31 (14.3)	18 (3.0)	4598 (1.0)
1500–2499	141 (16.1)	34 (15.7)	72 (11.9)	23,940 (5.0)
2500–3999	669 (76.5)	142 (65.4)	468 (77.6)	406,342 (85.6)
≥ 4000/unknown ^a	44 (5.0)	10 (4.6)	45 (7.5)	40,055 (8.4)
Tobacco use during pregnancy				
Yes	124 (14.2)	34 (15.7)	111 (18.4)	72,299 (15.2)
No	699 (80.0)	173 (79.7)	449 (74.5)	370,793 (78.1)
Unknown	51 (5.8)	10 (4.6)	43 (7.1)	31,843 (6.7)
Maternal education				
Less than high school	204 (23.3)	48 (22.1)	146 (24.2)	107,966 (22.7)
High school	319 (36.5)	77 (35.5)	233 (38.6)	165,269 (34.8)
More than high school/unknown ^a	351 (40.2)	92 (42.4)	224 (37.1)	201,700 (42.5)
Urbanization				
Rural	152 (17.4)	45 (20.7)	111 (18.4)	76,881 (16.2)
Urban	722 (82.6)	172 (79.3)	492 (81.6)	398,054 (83.8)

^a The Unknown category was combined with another category to ensure confidentiality following Oklahoma State Department of Health policies requiring suppression of categories with < 6 observations.

^b Categories with < 6 observations suppressed following Oklahoma State Department of Health policies (Neural Tube Defects column, Non-Hispanic Asian/Unknown row).

comparison with the McKenzie et al. (2014) analysis at 2-, 5-, and 10-mile buffers; 4) including records geocoded to the ZIP code centroid; and 5) using wells producing during the estimated month of conception based on gestational age at delivery (N = 462,654 children with reported gestational age at delivery). We conducted the analysis using estimated month of conception since congenital anomalies develop early in pregnancy (Czeizel et al., 2008; Selevan et al., 2000). Although we do not have information on residence at conception, we were able to determine the IDW for actively producing wells during an estimated month of conception using the month of birth and gestational age at delivery. Children missing gestational age at delivery from the birth record were excluded from this sensitivity analysis. To allow for a more direct comparison, we also conducted the analysis using the natural well activity during the month of birth excluding children with missing gestational age.

All analyses were conducted in SAS v. 9.4 and ArcGIS v. 10.4. We obtained Institutional Review Board approval from the University of

Oklahoma Health Sciences Center and the Oklahoma State Department of Health.

3. Results

We observed differences in demographic and birth characteristics between children with specific anomalies and those without anomalies (Table 1). Notable differences include a higher frequency of males for children with CCHD and oral clefts compared to those without anomalies. Children with all anomaly types were more frequently born at an earlier gestational age and children with CCHD and NTD had a lower birthweight compared to children without anomalies.

Producing natural gas well concentration from 1997 to 2009 was highest in the northwestern part of the state, with increased density also observed in southcentral and eastern Oklahoma (Fig. 2). The geographic distribution of producing natural gas wells by year in Oklahoma was fairly constant (data not shown), with a total of 417,110 unique

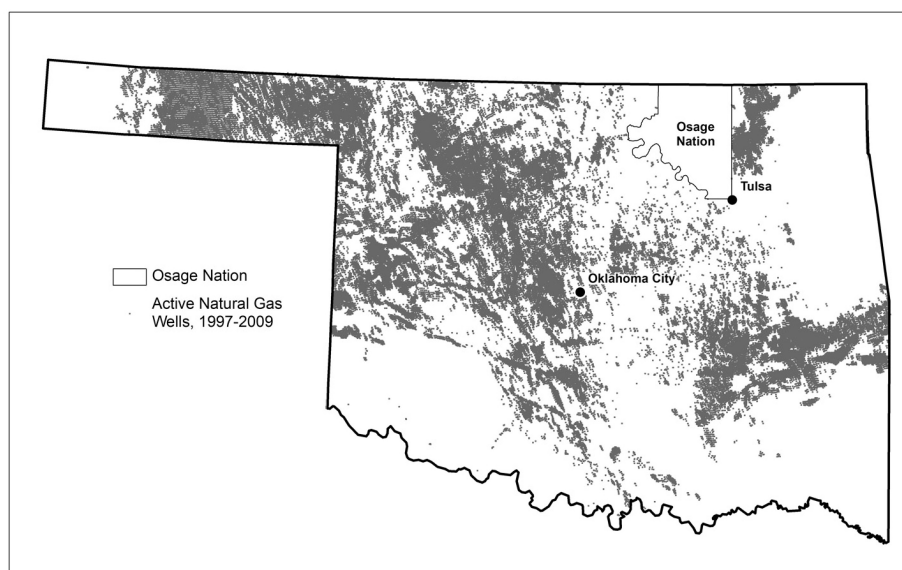


Fig. 2. Distribution of producing natural gas wells in Oklahoma from 1997 to 2009 (excluding Osage Nation). Sources: Natural Gas Wells: Oklahoma Corporation Commission; Oklahoma Freeways: Federal Highway Administration, National Transportation Atlas.

Table 2

Prevalence proportion ratios and 95% confidence intervals for the relationship between natural gas well activity within a 2-mile buffer of the birth residence and specific congenital anomalies (N = 476,600).

IDW summed well count by anomaly type	N with anomalies	Adjusted ^a PPR (95% CI)
Critical congenital heart defects	874	
0	494	Reference
0.25–1.88	132	1.02 (0.84, 1.24)
> 1.88–9.00	128	1.01 (0.83, 1.23)
> 9.00–47,679.13	120	0.91 (0.75, 1.11)
Neural tube defects	217	
0	114	Reference
0.25–1.88	28	0.89 (0.58, 1.37)
> 1.88–9.00	39	1.34 (0.93, 1.93)
> 9.00–47,679.13	36	1.20 (0.82, 1.75)
Oral clefts	603	
0	340	Reference
0.25–1.88	75	0.85 (0.67, 1.10)
> 1.88–9.00	94	1.06 (0.84, 1.34)
> 9.00–47,679.13	94	1.03 (0.82, 1.29)

IDW: Inverse Distance Weight, PPR: Prevalence proportion ratio, 95% CI: 95% confidence interval.

^a Adjusted for maternal education.

producing natural gas wells in Oklahoma over the study time period. The distribution of IDW well count indicates an increasing percentage of birth residences with no wells within the buffer as the buffer size decreases (Table S3).

We observed an increased prevalence of NTDs for those with natural gas activity in the 2nd (PPR: 1.34, 95% CI: 0.93, 1.93) and 3rd (PPR: 1.20, 95% CI: 0.82, 1.75) tertiles compared to birth residences with no wells in the 2-mile buffer after adjustment for maternal education (Table 2). However, the 95% confidence interval included the null value. We observed no association between natural gas activity at the 2-mile buffer and CCHDs or oral clefts. In an exploratory analysis, we evaluated the relationship between natural gas activity and specific CCHDs, NTDs, and oral clefts (Table 3). We observed an elevated prevalence of the following CCHDs among those with any natural gas activity compared to none, though the 95% confidence intervals included the null value: common truncus, transposition of the great arteries, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, interrupted aortic arch, and total anomalous pulmonary venous

connection. We also observed an increased PPR for spina bifida and cleft palate only, though the results were not statistically significant.

In our sensitivity analyses of 5- and 10- mile buffers around the birth residence and analyses adjusting for all potential covariates, we observed similar results as our primary analysis of a 2-mile buffer. However, the PPR for NTDs was attenuated at larger buffers and only elevated for the 3rd tertile after adjustment for maternal education (5-mile buffer PPR: 1.15, 95% CI: 0.81, 1.62; 10-mile buffer PPR: 1.19, 95% CI: 0.82, 1.73) (Table S4). When conducting analyses using the base distance (not squared) for all three buffers (Table S5), incorporating those who geocoded to the ZIP code centroid (Table S6), and evaluating actively producing wells during the estimated month of conception (Table S7), we observed little difference in the results compared to our primary analysis.

4. Discussion

We observed an increased PPR for the association between natural gas activity and NTDs among children in Oklahoma, though this was not statistically significant. This increased PPR was consistently observed in multiple sensitivity analyses. Our results support McKenzie et al. (2014), who observed an elevated odds of NTDs (OR: 1.9, 95% CI: 0.9, 4.3) among those with a natural gas activity in the 3rd tertile compared to no wells within 2 miles of the maternal residence at birth after adjustment for sex, parity, and maternal factors of age, ethnicity, smoking status, alcohol use, education, and elevation of residence. While results for 5- and 10-mile buffers in our study were attenuated compared to the 2-mile buffer, this is also consistent with McKenzie et al. (2014) in their analysis of multiple buffers and may indicate higher potential exposure to air, water, or other contaminants at smaller distances from the residence (McKenzie et al., 2012; Whitworth et al., 2017; Whitworth et al., 2018). The authors restricted their analysis to rural children (small towns with < 50,000 people), which differed from our population since we included births from the entire state. Although not statistically significant, McKenzie et al. (2014) observed a protective association among children with oral clefts (3rd v. 1st tertile OR: 0.8, 95% CI: 0.6, 1.2), which was not consistent with our results.

McKenzie et al. (2014) also reported an increased odds of congenital heart defects among those with natural gas activity in the 3rd tertile (OR: 1.3, 95% CI: 1.1, 1.5). The authors observed an elevated odds of

Table 3

Association between natural gas well activity within a 2-miles of the birth residence and specific critical congenital heart defects, neural tube defects, and oral clefts (N = 476,600).

IDW summed well count	N with anomalies	Unadjusted PPR (95% CI)	Adjusted ^a PPR (95% CI)
Specific critical congenital heart defects			
Common truncus			
0	24	Reference	Reference
> 0–47,679.13	22	1.15 (0.65, 2.06)	1.15 (0.64, 2.06)
Transposition of the great arteries			
0	64	Reference	Reference
> 0–47,679.13	57	1.12 (0.78, 1.60)	1.15 (0.80, 1.65)
Double outlet right ventricle			
0	20	Reference	Reference
> 0–47,679.13	12	0.75 (0.37, 1.54)	0.77 (0.38, 1.57)
Single ventricle			
0	37	Reference	Reference
> 0–47,679.13	30	1.02 (0.63, 1.65)	1.02 (0.63, 1.66)
Pulmonary valve atresia and stenosis			
0	22	Reference	Reference
> 0–47,679.13	26	1.49 (0.84, 2.62)	1.45 (0.82, 2.55)
Tricuspid valve atresia and stenosis			
0	17	Reference	Reference
> 0–47,679.13	17	1.26 (0.64, 2.46)	1.32 (0.66, 2.63)
Ebstein anomaly			
0	17	Reference	Reference
> 0–47,679.13	12	0.89 (0.42, 1.86)	0.95 (0.45, 2.00)
Hypoplastic left heart syndrome			
0	67	Reference	Reference
> 0–47,679.13	39	0.73 (0.49, 1.09)	0.76 (0.51, 1.13)
Coarctation of aorta			
0	126	Reference	Reference
> 0–47,679.13	100	1.00 (0.77, 1.30)	0.99 (0.76, 1.29)
Tetralogy of Fallot			
0	125	Reference	Reference
> 0–47,679.13	83	0.84 (0.63, 1.10)	0.85 (0.64, 1.12)
Interrupted aortic arch			
0	18	Reference	Reference
> 0–47,679.13	23	1.61 (0.87, 2.98)	1.57 (0.85, 2.92)
Total anomalous pulmonary venous connection			
0	34	Reference	Reference
> 0–47,679.13	41	1.52 (0.96, 2.39)	1.55 (0.98, 2.43)
Neural tube defects			
Spina Bifida			
0	88	Reference	Reference
> 0–47,679.13	85	1.21 (0.90, 1.64)	1.22 (0.91, 1.65)
Anencephaly			
0	26	Reference	Reference
> 0–47,679.13	18	0.87 (0.48, 1.59)	0.88 (0.48, 1.61)
Oral clefts			
Cleft lip only			
0	122	Reference	Reference
> 0–47,679.13	81	0.84 (0.63, 1.11)	0.85 (0.64, 1.12)
Cleft palate only			
0	195	Reference	Reference
> 0–47,679.13	174	1.12 (0.91, 1.38)	1.12 (0.92, 1.38)

IDW: Inverse Distance Weight, PPR: Prevalence proportion ratio, 95% CI: 95% confidence interval.

^a Adjusted for maternal education.

several specific heart defects using a 10-mile buffer including ventricular septal defects (Adjusted OR: 1.5, 95% CI: 1.1, 2.1), pulmonary artery and valve defects (includes pulmonary valve atresia and stenosis and pulmonary artery anomalies combined) (Adjusted OR: 1.6, 95% CI: 1.1, 2.2) and tricuspid valve defects (includes tricuspid valve atresia and stenosis and Ebstein's anomaly) (Adjusted OR: 4.2, 95% CI: 1.3, 13.0). Ventricular septal defects are not classified as CCHDs and, thus, were not evaluated in our study. At the 2-mile buffer using our definition of IDW, our results were consistent for pulmonary artery and tricuspid valve defects, though imprecise. Our study was the first to report an increased PPR for total anomalous pulmonary venous connection. Major differences between our analysis and that of McKenzie et al. (2014) include a focus on rural areas of Colorado and difference in the maximum IDW well score using the base distance (Colorado: 1400,

Oklahoma: 297 [Table S5]). The authors suggested that restriction to rural communities may limit the impact of urban air pollution on the study results. The difference in maximum IDW well count indicates more dense natural gas activity in rural Colorado than in Oklahoma and may indicate higher potential exposure in the rural Colorado population. Using the base distance would result in wells farther from the birth residence having a higher weight than those in our study. However, in our sensitivity analysis using this calculation for IDW (instead of the squared distance) at 2-, 5-, and 10-mile buffers, we observed little difference in our results.

Natural gas drilling has recently been evaluated with other perinatal outcomes, with mixed results (Casey et al., 2016; McKenzie et al., 2014; Stacy et al., 2015; Whitworth et al., 2017; Whitworth et al., 2018). A recent systematic review evaluated the relationship between oil and

natural gas drilling and reproductive health (Balise et al., 2016). The authors concluded that based on existing evidence, oil and gas drilling activities are harmful for human reproductive health, with stronger evidence for miscarriage, prostate cancer, congenital anomalies, and decreased semen quality than other evaluated health outcomes.

Strengths of our study include the use of a population-based registry for both congenital anomalies and births. OBDR is an active surveillance system, which works with all birthing hospitals in Oklahoma to obtain information on congenital anomalies following the National Birth Defects Prevention Network guidelines (National Birth Defects Prevention Network, 2004). We had information on all producing natural gas wells during the included birth years (excluding Osage Nation, see Methods). In addition, using the IDW method allowed us to retrospectively evaluate natural gas well activity within a specified buffer, which is individually calculated for each birth.

However, there are also limitations. One is the risk for survivor bias since not all children with anomalies will have survived to be included in our study and we only included live births in the analysis. This could potentially underestimate the association if natural gas activity is related to severe anomalies with high prenatal mortality. Because of small numbers of children with individual anomaly types, analyses at buffers smaller than 2 miles were infeasible for our study and limited our ability to evaluate tertiles of exposure for specific types of CCHDs, NTDs, and oral clefts. The inability to evaluate natural gas activity at smaller buffers may increase the risk of exposure misclassification. Because we did not conduct air sampling or collect biomarkers from mothers during pregnancy in our study, but instead, measured natural gas activity around the birth residence, there is a potential for misclassification. Additionally, mothers may not work near or in the home, which could result in an over or underestimate of the association depending on the location of the mother's workplace during pregnancy. Furthermore, we only have information on residence at birth, not residence during early pregnancy, which is the critical window of development for congenital anomalies (Czeizel et al., 2008; Selevan et al., 2000). However, we re-evaluated the association with natural gas activity during the month of conception using gestational age at delivery and observed similar results to our primary analysis. For this sensitivity analysis, we excluded approximately 3% of births with missing gestational age, which resulted in essentially no change in the distribution of birth and demographic characteristics by anomaly type. While our study is at risk for misclassification due to residential mobility during pregnancy, a recent study of ambient benzene exposure and congenital anomalies indicated the misclassification is likely non-differential, resulting in bias towards the null (Lupo et al., 2010). Future studies should incorporate residential history into the exposure assessment to minimize this potential bias.

In conclusion, we observed an increased, though imprecise, prevalence of NTDs and several specific CCHDs among those with increased natural gas activity compared to those with no activity within a 2-mile buffer of the birth residence. While this study supports the results of previous studies, further evaluation of the relationship between natural gas wells and both NTDs and CCHDs is necessary. In addition, evaluating how emissions differ with each phase of the drilling and production process are essential to improve exposure assessment. In addition, pooling data from multiple states with high natural gas production will allow researchers to better evaluate specific types of congenital anomalies. Future studies should also consider sampling air pollutants and water contaminants emitted during the natural gas drilling and production process to better understand the distribution of pollutants and the potential for maternal exposure during pregnancy.

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