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Congenital heart defects and intensity of oil and gas well site activities in early pregnancy

Lisa M. McKenzie[a,*], William Allshouse[a], Stephen Daniels[b]

[a] Department of Environmental and Occupational Health, Colorado School of Public Health, University of Colorado Anschutz Campus, Aurora, CO, USA
[b] Department of Pediatrics, University of Colorado School of Medicine, University of Colorado Anschutz Campus, Aurora, CO, USA

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ABSTRACT

Background: Preliminary studies suggest that offspring to mothers living near oil and natural gas (O&G) well sites are at higher risk of congenital heart defects (CHDs).
Objectives: Our objective was to address the limitations of previous studies in a new and more robust evaluation of the relationship between maternal proximity to O&G well site activities and births with CHDs.
Methods: We employed a nested case-control study of 3324 infants born in Colorado between 2005 and 2011. 187, 179, 132, and 38 singleton births with an aortic artery and valve (AAVD), pulmonary artery and valve (PAVD), conotruncal (CTD), or tricuspid valve (TVD) defect, respectively, were frequency matched 1:5 to controls on sex, maternal smoking, and race and ethnicity yielding 2860 controls. We estimated monthly intensities of O&G activity at maternal residences from three months prior to conception through the second gestational month with our intensity adjusted inverse distance weighted model. We used logistic regression models adjusted for O&G facilities other than wells, intensity of air pollution sources not associated with O&G activities, maternal age and socioeconomic status index, and infant sex and parity, to evaluate associations between CHDs and O&G activity intensity groups (low, medium, and high).
Results: Overall, CHDs were 1.4 (1.0, 2.0) and 1.7 (1.1, 2.6) times more likely than controls in the medium and high intensity groups, respectively, compared to the low intensity group. PAVDs were 1.7 (0.93, 3.0) and 2.5 (1.1, 5.3) times more likely in the medium and high intensity groups for mothers with an address found in the second gestational month. In rural areas, AAVDs, CTDs, and TVDs were 1.8 (0.97, 3.3) and 2.6 (1.1, 6.1); 2.1 (0.96, 4.5) and 4.0 (1.4, 12); and 3.4 (0.95, 12) and 4.6 (0.81, 26) times more likely than controls in the medium and high intensity groups.
Conclusions: This study provides further evidence of a positive association between maternal proximity to O&G well site activities and several types of CHDs, particularly in rural areas.

1. Introduction

Congenital heart defects (CHDs) are the most common type of birth defect in the United States (US) (Zoghbi and Jenkins, 2012). With an infant mortality rate of 41.46 per 100,000 live births, CHDs are the leading cause of death due to birth defects (Gilboa et al., 2010). Infants with a CHD are less likely to thrive, more likely to have developmental problems, and more vulnerable to brain injury (Gidding, 2012; Martinez-Biarge et al., 2013). Adults with a CHD are at increased risk of pulmonary hypertension, arrhythmias, infective endocarditis, anticoagulation, and congestive heart failure (Bhatt et al., 2015). Of the 1.5 million US adults living with a CHD, at least 500,000 need lifelong specialized care, with death and disability rates rising dramatically after 30 years of age (Zoghbi and Jenkins, 2012). Colorado's rate of 18.9 CHDs per 1000 births is more than twice the national rate of 8.1 CHDs per 1000 births (Brook et al., 2004).

Polygenic inherited disease, noninherited risk factors, or gene-environment interactions can result in congenital heart defects during the

Abbreviations: AAVD, aortic artery and valve defect; CDPHE, Colorado Department of Public Health and Environment; CHDs, congenital heart defect; CRCSN, Colorado Responds to Children with Special Needs; CTD, conotruncal defect; IA-IDW, intensity adjusted inverse distance weighted; IDW, inverse distance weighted; NO_2, nitrogen dioxide; O&G, oil and natural gas; OR, odds ratio; PAVD, pulmonary artery and valve defect; $PM_{2.5}$, particulate matter ≤ 2.5 μm; ppbv, parts per billion by volume; SES, socioeconomic status; TVD, tricuspid valve defect

* Corresponding author at: Department of Environmental and Occupational Health, Colorado School of Public Health, 13001 E. 17th Place, Campus Box B119, Aurora, CO 80045, USA.
E-mail address: Lisa.McKenzie@cuanschutz.edu (L.M. McKenzie).

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first 20–60 days of embryonic development (Jenkins et al., 2007). Less than 20% of CHDs are attributed to a genetic etiology and the contribution of non-inherited risk factors and gene-environment interactions to CHD etiology is not well understood (Fung et al., 2013; Kuehl and Loffredo, 2006). Animal models demonstrate that CHDs can occur with a single environmental exposure during early gestation (Linask, 2013). Many environmental risk factors have been associated with CHDs including maternal exposures (Jenkins et al., 2007) to hazardous air pollutants, such as benzene (Desrosiers et al., 2012; McMartin et al., 1998; Wennborg et al., 2005) diesel exhaust (Dadvand et al., 2011; Vrijheid et al., 2010) and stress (Adams et al., 1989; Carmichael and Shaw, 2000; Zhu et al., 2013).

One source of environmental exposures to hazardous air pollutants, diesel exhaust, and non-chemical stressors is the close proximity of oil and natural gas (O&G) wells to maternal residences (Adgate et al., 2014). Numerous studies have attributed increased hazardous air pollutant levels to O&G activities and have observed that emissions increase significantly during specific activities, such as well completions and during maintenance (Allen et al., 2013; Gilman et al., 2013; Halliday et al., 2016; Helmig et al., 2014; McKenzie et al., 2012; Pétron et al., 2012; Pétron et al., 2014). Some of the most common hazardous air pollutants (e.g., benzene, toluene and xylenes) emitted from O&G well sites are suspected teratogens (Colborn et al., 2011) that are known to cross the placenta (Shepard, 1995). In the summer of 2014, continuous ambient benzene sampling in Colorado's Denver Julesburg Basin indicated that mean benzene concentrations at night, when people are most likely to be at home, were on average twice the daytime mean (Halliday et al., 2016). Daytime benzene concentrations reached 120 parts per billion by volume (ppbv) in grab samples collected within 500 ft of O&G sites (McKenzie et al., 2018). Additionally, O&G operators use trucks with diesel engines to transport supplies, water, and waste to and from O&G wells, with 40 to 280 truck trips per day per well pad during development (Allshouse et al., 2019; Witter et al., 2013). Generators equipped with diesel engines are used both to drill wells and for hydraulic fracturing (King, 2012). Air pollutants in the diesel exhaust emitted from these trucks and generators include nitrogen dioxide (NO_2) and particulate matter ≤ 2.5 μm ($PM_{2.5}$) (Birch and Cary, 1996; Sydbom et al., 2001). Reactions between NO_2 and volatile organic compounds produce lead to ground level ozone production (US Environmental Protection Agency, 2018). Finally, non-chemical stressors, such as traffic, noise, light, and psychological stress, associated with O&G development may increase maternal stress levels and the risk of CHDs (Allshouse et al., 2019; Blair et al., 2018a,b; Malin et al., 2018; Witter et al., 2013).

In our previous retrospective cohort study of 124,842 births in rural Colorado between 1996 and 2009, we observed that the birth prevalence of CHDs increased with increasing density of O&G wells around the maternal residence, with an odds ratio of 1.3 for the highest exposure group compared to the referent group (95% CI: 1.2, 1.5) (McKenzie et al., 2014). A second retrospective study of 476,000 births in Oklahoma observed positive, but imprecise, associations between density of natural gas wells and several specific CHDs (conotruncal, pulmonary valve and artery, aortic arch, and tricuspid valve defects) (Janitz et al., 2018). These previous studies had three major limitations. First, they were not able to provide sufficient spatial and temporal granularity to assign exposures to the three months prior to conception and the first two months of gestation – the critical period of development for the fetal heart. Second, they were not able to distinguish between well development and production phases or account for varying activities on O&G well sites. Third, they did not confirm specific types of CHDs by a medical record review.

Our objective in this study was to address the limitations of these previous studies in a new and more robust evaluation of the relationship between maternal proximity to O&G well site activities and births with CHDs.

2. Methods

We conducted a nested case-control study of 3324 mother-infant pairs born in Colorado between 2005 and 2011 using de-identified data provided by the Colorado Department of Public Health and Environment's (CDPHE) Center for Health and Environmental Data. CDPHE de-identified the data to maintain the confidentiality of registry records.

2.1. Study population

Our population includes all live singleton births occurring between 2005 and 2011 to mothers living in 34 Colorado counties with 20 or more wells drilled (well starts) from 2004 to 2011 per 10,000 births (Supplemental Table 1). The cut-point of 20 or more well starts best captures counties in areas of intense O&G activity. We selected these inclusion criteria to focus our analysis on growth of unconventional O&G development, characterized by the use of hydraulic fracturing and/or directional drilling (Haynes et al., 2017). It was necessary to restrict the cohort to Colorado counties with active O&G development because most Coloradoans do not live near O&G wells: 6% of Coloradoans live with one mile of a well that was drilled after the year 2000 (McKenzie et al., 2016). Restricting the cohort to births in counties with 20 or more well starts per 10,000 births reduces skewing the distribution of births towards unexposed mothers. We excluded siblings of cases and controls. From this cohort, CDPHE staff selected cases and controls as described in the next section and shown in Fig. 1.

2.2. Case and control selection

CDPHE staff used the Colorado Responds to Children with Special Needs (CRCSN) birth defects registry to select cases from the cohort described above and in Fig. 1. The CRCSN includes children with birth defects identified from hospital records, the Newborn Genetics Screening Program, the Newborn Hearing Screening Program, laboratories, physicians, and genetic, developmental and other specialty clinics up to age 3 years. Children in our cohort that also were in the CRCSN birth defects registry and confirmed via a medical record review to have one of the following four specific types of CHDs, without a chromosomal anomaly, were selected as cases. The four specific types of CHDs are: (1) pulmonary artery and valve defects (PAVDs) defined as pulmonary valve atresia and stenosis and pulmonary artery anomalies with and without ventricular defects (ICD-9-CM 746.01, 746.02, 747.3, 747.31, 747.32, 747.39); (2) aortic artery and valve defects (AAVD) defined as aortic valve stenosis and coarctation of aorta with and without ventricular defects (746.3, 747.10); (3) conotruncal defects (CTDs) defined as Tetralogy of Fallot and transposition of great vessels with and without ventricular defects (745.2, 745.10, 745.11, 745.12, 745.19); and (4) tricuspid valve defects (TVDs) defined as tricuspid valve atresia and stenosis and Ebstein's anomaly with and without other CHDs (746.1, 746.2). Based on previous studies, we grouped CHDs into these specific clinical diagnostic groupings to increase statistical power and to enable comparisons with previous studies (Gilboa et al., 2005; Janitz et al., 2018; McKenzie et al., 2014; Ritz et al., 2002). Children with multiple types of CHDs were selected as cases for each specific type of CHD present. For example, a child diagnosed with both a CTD and PAVD, would be selected as both a CTD and PAVD case. Based on these criteria and definitions, 187, 179, 132, and 38 children with an AAVD, PAVD, CTD, or TVD, respectively, were selected as cases.

For each case, CDPHE staff selected five controls from the birth certificate data in Colorado Vital Statistics Program frequency matching 1 to 5 on sex (Vereczkey et al., 2013), maternal cigarette use during pregnancy (yes or no) (Malik et al., 2008), and combined race and ethnicity (Jenkins et al., 2007). For children with multiple ICD-9-CM codes for the same type of CHD described above, five controls were selected for each ICD-9-CM code. Thus, 2860 children were selected as

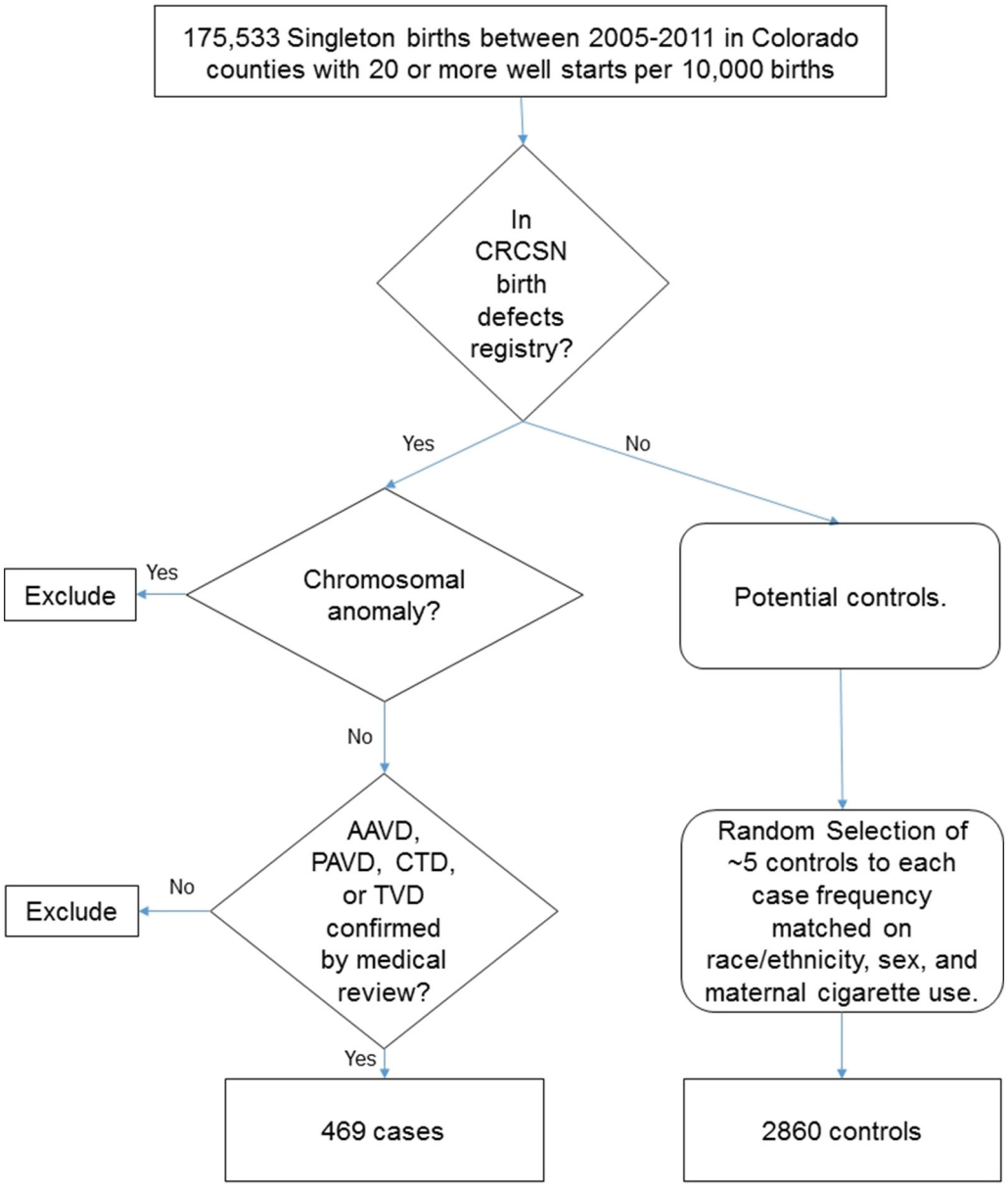

Fig. 1. Selection of cases and controls born between 2005 and 2011 in Colorado Countries with 20 or more active O&G wells.
AAVD: arterial artery or valve defect, CRCSN: Colorado Responds to Children with Special Needs, CTD: conotruncal defect: PAVD: pulmonary artery or valve defect; TVD: tricuspid valve defect.

controls. We compared each specific type of CHD to the entire control population.

2.3. Intensity of O&G well activity

Using information available in the publically accessible Colorado Oil and Gas Information System, we built a geocoded data set that contains the American Petroleum Institute well identification number, latitude, longitude, and status (development, producing, shut-in, and abandoned) of all O&G wells in Colorado between 2004 and 2011 (Colorado Oil and Gas Information System, 2015). To this data set, we added the latitude and longitude coordinates for O&G facilities other than wells (e.g. compressor stations, tank farms, and gathering lines) in the Colorado Oil and Gas Information System. We also added air pollution sources not associated with O&G activities in the US Environmental Protection Agency's Toxic Release Inventory program and Enforcement and Compliance History on-line data database (https://echo.epa.gov/facilities/facility-search); the US Geological Survey National Mines Information Center; and the CDPHE's Concentrated Animal Feeding Operations, and Composting, Solid Waste, and Wastewater Treatment Facility data. The final data set was then parsed into months (84 months from 2004 to 2011) and provided to CDPHE staff.

For each case and control, CDPHE staff identified all O&G wells, O&G facilities other than wells, and air pollution sources not associated with O&G activities within 10 miles of the maternal residence provided on the birth certificate for each month in the three months prior to conception through the second month of gestation (five months). Based on associations observed with adverse health outcomes in previous studies, a 10-mile buffer represents a conservative geographic area of interest that could plausibly affect exposure (McKenzie et al., 2014, 2017; Stacy et al., 2015). We included the 3-months prior to conception in our exposure assessment because of the possibly mutation generation during ovum cell formation (Shi and Chia, 2001) or epigenetic modifications transmitted through sperm DNA, histones, and RNA (Braun et al., 2017). CDPHE staff determined the three months prior to conception through the second month of gestation period from the birth

date and gestational age recorded on the birth certificate. CDPHE staff also computed distances between the maternal residence and each O&G well, O&G facility other than a well, and air pollution source not associated with O&G activities using spherically-adjusted straight line distances and returned to us a de-identified data set.

Next, we applied our intensity adjusted inverse distance weighted (IA-IDW) model, as described in Allshouse et al. (2017), to estimate the monthly relative intensity of O&G well site activity around the maternal residence of each case and control for each month from three months prior to conception through the second month of gestation. Because the O&G wells included in our IA-IDW exposure metric are weighted by distance between the well and the residence, a well that is closer to the individual will contribute more to that individual's metric than a well with the same intensity that is further away. Our IA-IDW metric differs from other methods that define an individual as exposed if they have a well within a given buffer without adjustment for phase of well development or intensity of operations that occur at the well site (Currie et al., 2017; Hill, 2018).

2.4. O&G facilities other than wells

For O&G facilities other than wells, we used an inverse distance weighted (IDW) approach, commonly used to estimate individual air pollutant exposures from multiple fixed locations (Brauer et al., 2008; Ghosh et al., 2012; McKenzie et al., 2014, 2017) to estimate maternal exposure. We separately calculated the IDW count of all existing O&G facilities that were not on a well site for each month between three months prior to conception through the second month of gestation within a 10-mile radius of each maternal residence:

$$IDW\ count = \sum_{i=1}^{n} \frac{1}{d_i^2} \quad (1)$$

where

d_i = distance of the ith individual well from maternal residence.
n = number of O&G facilities other than well sites within a 10-mile radius.

2.5. Air pollution sources not associated with O&G activities

For air pollution sources not associated with O&G activities, we calculated an intensity adjusted inverse distance weight (IA-IDW) count for each month between three months prior to conception through the second month of gestation within a 10-mile radius of each maternal residence:

$$IA - IDW\ count = \sum_{i=1}^{n} \frac{I}{d_i^2}$$

where:

d_i = distance of the ith individual well from maternal residence.
n = number of air pollution sources not associated with O&G activities within a 10-mile radius.
I = relative intensity of emissions or activities.

We assigned concentrated animal feeding operations an intensity of 1–5 based on the percentile of animal units; mining sources an intensity of 1–4 based on the type of mine (Supplemental Table 2); and Toxic Release Inventory and Solid Waste, and Wastewater Treatment Facility sources an intensity of 1–5 based on the percentile of annual air emissions and waste flow, respectively. We assigned Composting and Enforcement and Compliance History sources an intensity of 1 due lack of information on emissions and activity.

2.6. Maternal residence in three months prior to conception through second week of gestation

We conducted all residential history searches on the CDPHE campus under the supervision of CDPHE staff. CDPHE released no personal identifiers to our research team. We used the mother's and father's (if available) name and birth date recorded on the birth certificate to perform a maternal residential history search for the year preceding the child's birth date in the LexisNexis® Accurint® for Government data system (LexisNexis®) and provided the results of the search to CDPHE staff. LexisNexis® uses data linking technologies that enable searches of current comprehensive and authoritative public records information. If the residential history search found the maternal address did not change between three months prior to the pregnancy to the birth date or if we could not determine the maternal residence in this time-period, CDPHE staff used the address on the birth certificate to calculate the IDW-metrics. If the residential history search found the maternal address differed from the address on the birth certificate at any point during the three months prior to conception through the second month of gestation, the address(es) found in the residential history search were used to calculate IDW-metrics.

2.7. Statistical analysis

We log-transformed All IDW-metrics because the distribution of each of our IDW metrics were highly skewed with long tails towards large values. Based on multi-modal log transformed distributions for IA-IDW and IDW counts of O&G facilities other than wells, we divided the distributions of these IDW-metrics into low, medium, and high exposure groups based on modal cut points for subsequent statistical analysis. We divided the final IA-IDW well distribution into low, medium, and high exposure groups using cut points of 1 and 403 intensity well counts per square mile (mile^2) (Supplemental Fig. 1). We divided the final IDW count for O&G facilities other than wells into low, medium, and high groups using cut points of 1 and 6 IDW counts/mile^2 (Supplemental Fig. 2). We used the continuous log-transformed data for IA-IDW count of air pollution sources not associated with O&G activities for subsequent statistical analysis because the log-transformed data approximated a Gaussian distribution (Supplemental Fig. 3).

We used data from the 2007–2011 American Community Survey 5-year estimates to calculate a composite socioeconomic status (SES) index at the zip-code level, based on a principal component analyses method presented in Yost et al., 2001 and applied in other studies (Cheng et al., 2010; Ghosh et al., 2012, 2013; Yost et al., 2001). We included seven indicator variables in the principle component analysis: percent in food stamps or Supplemental Nutrition Assistance Program, percent below poverty level, percent on public cash assistance, percent unemployed, median household income, median house value, and educational attainment for adults > 25 years. We divided educational attainment into three groups: no high school degree, high school degree and some college, and bachelor degree or higher. The first two components captured 60% of the variability with eigenvalues > 1. Because the first component best reflected SES disadvantage, we used the first component to create our SES index. The first component captured 42% of the variability with each indicator loading as follows (correlation coefficient of each indicator with the SES index in parentheses): percent on food stamps or Supplemental Nutrition Assistance Program (0.48); percent below poverty (0.41); percent public cash assistance (0.34); percent unemployed (0.30); median household income (−0.44); median household value (−0.37); and educational attainment (−0.28). Therefore, a larger SES index represents a lower SES level. Lastly, we grouped the SES indices into quantiles (Yost et al., 2001).

For each of the five months between three months prior to conception through the second month of gestation, we used unconditional logistic regression (Jewell, 2004; Mansournia et al., 2018) to evaluate associations between each dichotomous outcome (combined CHDs,

AAVD, PAVD, CVD, and TVD) and IA-IDW group with the low group as the referent. First, we estimated the crude odds ratio (OR) associated with IA-IDW exposure group for each binary outcome. We further used logistic regression to investigate for associations by adjusting for potential confounders, as well as child covariates, based on a priori knowledge of their association with both exposure and/or outcome. Specifically, we considered the following co-variates: maternal age (continuous) (Reefhuis and Honein, 2004), parity (0, 1, 2, > 2) (Vereczkey et al., 2013), SES index (quantile), sex (Vereczkey et al., 2013), IDW count of O&G facilities other than wells (low, medium, high), and IA-IDW count for air pollution sources not associated with O&G activities (continuous). Because our previous study excluded urban populations (McKenzie et al., 2014), we tested for effect modification of residence in a rural zip code. Additionally, we tested for effect modification by infant sex, evaluated a 2-mile buffer, evaluated an analysis of IA-IDW > 0 divided into tertiles with a referent group with no O&G wells in the 10-mile buffer, and evaluated year of birth as a confounder. We performed sensitivity analyses on two subsets of our study population: mother's address in the second gestational month found in LexisNexis® and exclusion of births to mothers in the O&G facilities other than wells high group. We conducted tests to evaluate linear trends in binominal proportions with increasing IA-IDW by treating the categorical IA-IDW variable as ordinal and used the Wald Chi-Square parameter to test for statistical significance (Carlton et al., 2015). With the exception of effect modification, we considered the statistical significance of the association, as well as the trend, in evaluating results, at an alpha of 0.05. We evaluated effect modification based on differences in effect size in stratified analyses. The Colorado Multi-Institutional Review Board approved our study protocol (Protocol Number: 14-1343).

3. Results

Table 1 summarizes the characteristics of our population by case and control status. A higher proportion of infants with an AAVD were male, had a white non-Hispanic mother, or had a mother living in a more advantaged SES group than controls. A higher proportion of infants with a PAVD were female, first born, had a mother living in a less advantaged SES group, or had fewer O&G facilities other than wells in the 10-mile buffer than controls. A higher proportion of infants with a CTD were first born, had a mother living in a less advantaged SES group, and a higher density of O&G facilities other than wells in the 10-mile buffer around the mother's residence than controls. A higher proportion of infants with a TVD were female, had older siblings, had mothers living in a rural area, had less intensity of air pollution sources not associated with O&G activity, or less density of O&G facilities other than wells in the 10-mile buffer around the mother's residence than controls. Additionally, we were more likely to find a residential history for mothers of infants with a CHD than controls.

Table 2 summarizes our study population's characteristics by exposure status (IA-IDW well count within a ten mile buffer of the mother's residence in the second gestational month). Most infant-mother pairs (59%) were in the medium exposure group, followed by the low (25%) and high (15%) exposure groups. Estimated exposures, as represented by IA-IDW well counts, tended to be lower for male infants and mothers in a higher SES group, in a rural area, or with lower densities of O&G facilities other than wells or air pollution sources not associated with O&G activities in the 10-mile buffer around their residence. Additionally, we were less likely to find a residential history for mothers in the low exposure group.

3.1. Overall results

Both crude and adjusted estimates indicate an increase in odds of maternal exposure to O&G well site activities in the second gestational month, as represented by IA-IDW well counts, in births with any CHD (Table 3). Congenital heart defects were 1.4 (95% CI: 1.0, 2.0) and 1.7 (95% CI: 1.1, 2.6) times more likely than controls in the medium and high exposure groups, respectively, compared to the least exposed group after adjustment (p for trend = 0.0230). Similarly, both crude and adjusted estimates indicate an increase in odds of maternal exposure to O&G well site activities in the second gestational month, as represented by IA-IDW well counts, in births with a CTD or PAVD. Births with a CTD were 1.5 (95% CI: 0.87, 2.6) and 2.0 (95% CI: 0.97,

Table 1
Study population characteristics for cases and controls born between 2005 and 2011 in Colorado counties with 20 or more O&G well starts per 10,000 births.

Maternal or infant characteristic	AAVD cases[c]	PAVD cases[c]	CTD cases[c]	TVD cases[c]	Controls
Total N	187	179	132	38	2860
Maternal age (years)					
Median	29	27	27	28	27
25th Percentile	23	23	22	24	23
75th Percentile	34	32	32	33	32
Maternal combined race and ethnicity (%)[b]					
White – Non-Hispanic	63	57	58	58	59
White – Hispanic	28	34	31	32	32
Other	5.4	7.3	10	11	7.7
Missing	3.2	1.7	1.5	0	1.2
Male (%)	59	48	56	47	54
Maternal smoking (%)					
No	91	91	86	92	89
Missing	0	0	0	0	< 1
Change in maternal address between 3 months prior to conception to birth of child (%)					
No	74	69	70	71	67
Yes	8.0	5.6	9.1	7.9	9.0
Unknown	18	25	21	21	24
Parity (%)					
0	37	41	46	34	39
1	29	32	27	34	33
2	21	16	13	16	18
> 2	13	10	13	16	10
Rural (%)	60	60	55	68	62
SES Index Percentile (%)					
20	23	17	17	21	20
40	21	13	13	24	20
60	21	21	18	13	21
80	19	28	27	13	20
100	16	21	25	29	20
Missing	0	< 1	0	0	< 1
IDW Group of O&G Facilities other than wells (%)[a]					
Low	36	39	42	42	36
Medium	27	27	23	21	28
High	36	35	36	37	37
IA-IDW count of air pollution sources not associated with O&G activities (intensity/mile^2)					
Median	5.1	6.7	6.2	5.4	5.9
25th Percentile	3.2	3.6	3.3	3.6	3.3
75th Percentile	11	12	11	7.9	11
IA-IDW group (%)[b]					
Low	21	25	26	29	26
Medium	64	59	56	58	58
High	14	16	18	13	15

AAVD = Aortic artery and valve defects, CTD = conotruncal defects, IA-IDW = intensity adjusted inverse distance weighted well count, IDW = inverse distance weighted count, N = number, O&G = oil and natural gas, PAVD = Pulmonary artery and valve defects, TVD = tricuspid valve defects.

[a] Low = < 1 O&G facilities per square mile, medium = 1 to 6 other types of O&G facilities per square mile, high = > 6 other types of O&G facilities per square mile.

[b] Low = < 1 intensity wells per square mile, medium = 1 to 403 intensity wells per square mile, high = > 403 intensity wells per mile.

[c] The sum of AAVD, PAVD, CTD, and TVD cases is > 469 because a few infants had multiple CHDs.

Table 2
Study population characteristics for cases and controls born between 2005 and 2011 in Colorado counties with 20 or more O&G well starts per 10,000 births by IA-IDW group.

	IA-IDW group		
	Low[a]	Medium[a]	High[a]
Total (N)	864	1945	515
Maternal age (years)			
Median	26	28	27
25th Percentile	22	23	23
75th Percentile	31	32	32
Maternal combined race and ethnicity (%)			
White – Non-Hispanic	57	61	56
White – Hispanic	34	30	37
Other	7.4	8.1	6.2
Missing	1.3	1.4	1.4
Male (%)	52	55	55
Maternal smoking (%)			
No	88	90	89
Missing	0	< 1	< 1
Change in maternal address between 3 months prior to conception to birth of child (%)			
No	57	72	69
Yes	14	7.0	8.4
Unknown	29	21	22
Parity (%)			
0	36	41	38
1	33	33	30
2	20	16	19
> 2	11	8.8	13
Rural (%)	75	61	42
SES Index Percentile (%)			
20	17	21	18
40	13	22	23
60	18	21	26
80	22	22	10
100	31	14	24
Missing	< 1	0	0
IDW group of O&G facilities other than wells (%)[b]			
Low	94	20	< 1
Medium	5.6	38	22
High	< 1	42	78
IA-IDW Count of Air Pollution Sources not associated with O&G activities (source/mile^2)			
Median	4.5	6.1	7.8
25th Percentile	1.4	3.3	4.9
75th Percentile	8.2	10	14

IA-IDW = intensity adjusted inverse distance weighted well count, IDW = inverse distance weighted count, N = number, O&G = oil and natural gas, SES = social-economic status.

[a] Low = < 1 intensity wells per square mile, medium = 1 to 403 intensity wells per square mile, high = > 403 intensity wells per mile.

[b] Low = < 1 O&G facilities per square mile, medium = 1 to 6 other types of O&G facilities per square mile, high = > 6 other types of O&G facilities per square mile.

4.3) times more likely than controls in the medium and high exposure groups, respectively, compared to the least exposed group (p for trend = 0.0599). Births with a PAVD were 1.4 (95% CI: 0.87, 2.3) and 1.7 (95% CI: 0.87, 3.2) times more likely than controls in the medium and high exposure groups, respectively, compared to the least exposed group (p for trend = 0.1234). While both crude and adjusted estimates indicate increased odds of births with AAVDs and TVDs with increasing maternal exposure to O&G well site activities in the second gestational month, we did not observe a trend from low to high exposure.

We observed similar associations for AAVDs and attenuated associations for CTDs and TVDs with exposure to O&G well site activities in each of the three months prior to conception through the first gestational month for AAVDs (Supplemental Tables 3–6). For PAVDs, we observed the strongest association with exposures in the two months prior to conception (Supplemental Table 4).

In our evaluation of a 2-mile buffer zone around the maternal residence in the second month of gestation, we observed similar results for AAVDs, stronger associations for CTDs and TVDs, and attenuation towards the null for PAVDs (Supplemental Table 7). In our evaluation of IA-IDW well count > 0 divided into tertiles with a referent group as no O&G wells in the 10-mile buffer, we observed some bias towards the null for the AAVD and TVD outcomes and potentially some bias away from the null for the CTD and PAVD outcomes (Supplemental Table 8). Further adjustment of our models for year of birth did not change our results (Supplemental Table 9).

3.2. Effect modification and stratified results

Our finding of stronger associations between odds of a birth with a CHD and maternal exposure to O&G well site activities for mothers with a residence in a rural zip code compared to an urban zip code indicates effect modification (Table 4). In rural zip codes, CHDs, AAVDs, CTDs, and TVDs in the medium and high exposure groups were 1.6 (95% CI: 1.0, 2.4) and 2.4 (95% CI: 1.3, 4.4, p for trend = 0.0033); 1.8 (95% CI: 0.97, 3.3) and 2.6 (95% CI: 1.1, 6.1, p for trend = 0.0.0276); 2.1 (95% CI: 0.96, 4.5) and 4.0 (95% CI: 1.4, 12, p for trend = 0.0108); and 3.4 (95% CI: 0.95, 12) and 4.6 (95% CI: 0.81, 26, p for trend = 0.0846) times more likely, respectively, than controls compared to the least exposed group after adjustment for co-variates. With the exception of PAVDs, we observed no associations between O&G exposure and CHDs in births to mothers residing in an urban zip code. While we did not observe effect modification between exposure and infant sex, we did observe stronger associations between maternal exposure to O&G well activity and AAVDs, PAVDs, and CTDs in female infants (Supplemental Table 10).

3.3. Sensitivity analyses

In our sensitivity analyses of births to mother's for whom we found a residential address in the second gestational month and exclusion of births to mother's in the O&G facilities other than wells high group, we observed results similar to the whole population, with the following exception (Supplemental Tables 11 and 12). With exclusion of births for which we could not find the mother's address in the second gestational month, the association between exposure to O&G well activities and PAVDs increased. Compared to controls, births to mothers in the medium and high exposure groups had a 1.7 (95% CI: 0.93, 3.0) and 2.5 (95% CI: 1.1, 5.3, p for trend = 0.0243) times higher prevalence of PAVDs, respectively, for mothers with a found address in the second gestational month after adjusting for co-variates.

4. Discussion

We observed positive associations between odds of a birth with a CHD and maternal exposure to O&G well activities, as represented by IA-IDW well counts, in the second gestational month. The odds of a birth with any type of CHD increased from the low to high exposure group. In rural areas, odds of a birth with an AAVD, CTD, or TVD were 2.6–4.6 times more likely than controls in the high exposure group compared to the low exposure group. In urban areas, we did not observe associations between odds of a birth with an AAVD, CTD, or TVD. In the subset of births for which we were able to find the maternal address in the second gestational month, odds of a birth with a PAVD were 2.5 times more likely than controls in the high exposure group.

Interestingly, we observed associations between maternal exposures to O&G well site activities and AAVDs, CTDs, and TVDs in rural areas and not in urban areas. The 62% of mothers in our study living in a rural area differed from mothers living in urban areas in several ways.

Table 3
Association between intensity adjusted O&G well site activity within ten-mile radius of maternal residence in second month of pregnancy and congenital heart defects for cases and controls born between 2005 and 2011 in Colorado counties with 20 or more O&G well starts per 10,000 births.

IA-IDW group[a]	Low	Medium	High	Trend test p-value[c]
Controls (N)	751	1669	438	
Any CHD				
Cases (N)	110	276	77	
Crude OR	Referent	1.1 (0.89, 1.4)	1.2 (0.88, 1.6)	
Adjusted OR (95% CI)[b]	Referent	1.4 (1.0, 2.0)	1.7 (1.1, 2.6)	0.0230
AAVDs				
Cases (N)	40	120	27	
Crude OR	Referent	1.4 (0.93, 2.0)	1.2 (0.70, 1.9)	
Adjusted OR (95% CI)[b]	Referent	1.6 (1.0, 2.6)	1.5 (0.79, 3.0)	0.2373
PAVD				
Cases (N)	43	106	29	
Crude OR	Referent	1.1 (0.77, 1.6)	1.2 (0.71, 1.9)	
Adjusted OR (95% CI)[b]	Referent	1.4 (0.87, 2.3)	1.7 (0.87, 3.2)	0.1234
CTD				
Cases (N)	34	74	24	
Crude OR	Referent	0.98 (0.65, 1.5)	1.2 (0.71, 2.1)	
Adjusted OR (95% CI)[b]	Referent	1.5 (0.87, 2.6)	2.0 (0.97, 4.3)	0.0599
TVD				
Cases (N)	11	22	5	
Crude OR	Referent	0.90 (0.43, 1.9)	0.78 (0.27, 2.3)	
Adjusted OR (95% CI)[b]	Referent	1.4 (0.49, 4.1)	1.1 (0.25, 4.8)	0.9478

AAVD = Aortic artery and valve defects, CHD = congenital heart defects, CTD = conotruncal defects, IA-IDW = intensity adjusted inverse distance weighted well count, N = number, O&G = oil and natural gas, PAVD = Pulmonary artery and valve defects, TVD = tricuspid valve defects.

[a] Low = 0 to < 1 intensity wells per square mile; medium = 1 to < 403 intensity wells per square mile, high = ≥ 403 intensity wells per square mile.

[b] Adjusted for IDW count of oil and gas facilities other than wells in 10-mile buffer, IA-IDW count of air pollution sources not associated with O&G activities, maternal age, and SES group, as well as infant parity and sex.

[c] Trend tests performed by treating categorical inverse-distance well count as an ordinal.

In rural areas, mothers were younger and a higher proportion were white non-Hispanic, in a less advantaged SES group, and had less density of O&G facilities other than wells and less intensive O&G well site activities around their home (Tables 1 and 2). Additionally, the median IA-IDW count of air pollution sources not associated with O&G activities within 10 miles of the mother's home was lower in rural areas, even though we observed the maximum IA-IDW count for these air pollution sources in a rural zip code. Because we would expect more air pollution sources in urban areas than rural areas, we performed an exploratory analysis for effect modification of IA-IDW counts of air pollution sources not associated with O&G activities on IA-IDW well count. Our exploratory analysis indicates that the intensity of air pollution sources not associated with O&G activities modifies the effect of the intensity of O&G well site activity on CHD prevalence. Stratifying our population by tertile of IA-IDW count of air pollution sources not associated with O&G activities indicates a possible additive effect: the association between CHDs and intensity of O&G well site activities strengthens in areas with higher densities of other air pollution sources (Table 5). Therefore, we suspect that both residual confounding and confounding from air pollution sources not considered in our study (e.g. traffic related pollution and gasoline stations) may have obscured associations particularly in urban areas. We did not observe effect modification between IA-IDW exposures groups and other covariates (ethnicity, SES group, and O&G facilities other than wells).

Previous retrospective cohort studies of mother-infant pairs in Oklahoma and rural Colorado also indicated positive associations between CHDs and maternal proximity to O&G well sites (Janitz et al., 2018; McKenzie et al., 2014) albeit the associations were smaller than observed in our study. Our ability to confirm the maternal residence, estimate the intensity of O&G well activities, and confirm contributions from other O&G facilities and sources of air pollution, around the maternal residence during the critical period for CHD development likely reduced exposure misclassification that may have attenuated these previous study results towards the null. Additionally, our CHD cases were confirmed by medical record review and did not include CHDs with a known genetic origin, thus reducing the potential for outcome misclassification. Finally, we adjusted our results for SES using an SES index for the mother's zip code. While an SES index is a more robust approach than use of maternal education as a proxy for SES, there is likely some misclassification due to aggregation to the zip code level.

O&G well site activities are a known source of $PM_{2.5}$, NO_2, and hazardous air pollutants (Allshouse et al., 2019; Collett et al., 2016; Duncan et al., 2016; Evanoski-Cole et al., 2017; Helmig et al., 2014; Hildenbrand et al., 2016; McCawley, 2015; Roy et al., 2013) and are known to have short periods of high emissions (Allen et al., 2017; Halliday et al., 2016). Our results are in general agreement with epidemiological studies suggesting associations between maternal exposures to these air pollutants and CHDs (Stingone et al., 2017; Dadvand et al., 2011; McMartin et al., 1998; Wennborg et al., 2005). Studies evaluating specific types of CHDs suggest relationships between maternal NO_2 exposures with AAVDs (coarctation of the aorta), PAVDs (pulmonary valve stenosis) and CTDs (tetralogy of Fallot) (Schembari et al., 2014; Stingone et al., 2014; Vrijheid et al., 2010). Studies also indicate and association between maternal $PM_{2.5}$ exposures and AAVDs, PAVDs, and CTDs (Tanner et al., 2015; Warren et al., 2016; Padula et al., 2013; Zhang et al., 2016). Other studies suggest an association between maternal occupational exposures to Stoddard solvents and CTDs (transposition of the great arteries), AAVDs (aortic valve stenosis), and PAVDs (pulmonary valve stenosis) (Gilboa et al., 2012).

While the biological mechanism between maternal exposures to environmental stressors such as air pollutants and CHDs is not entirely understood, the available evidence indicates that environmental stressors may create oxidative stress in embryonic cells during formation of the cardiac neural crest in the second gestational month, ultimately resulting in teratogenesis (Badham et al., 2010; Hansen, 2006; Wu et al., 2016). Most non-genetic CTDs are a direct result and most non-genetic PAVDs and AAVDs are an indirect result of perturbations in cardiac neural crest formation (Rosenquist, 2013). Because of rapid

Table 4
Association between intensity adjusted O&G well site activity within ten-mile radius of maternal residence in second month of pregnancy and congenital heart defects for cases and controls born between 2005 and 2011 in Colorado counties with 20 or more O&G well starts per 10,000 births stratified by rural and urban zip codes.

IA-IDW[a]	Rural zip codes				Urban zip codes				Effect modification between rural and IA-IDW group p-value
	Low	Medium	High	Trend test p-value[c]	Low	Medium	High	Trend test p-value[c]	
Controls (N)	571	1032	178		180	637	260		
Any CHD									
Cases (N)	73	160	39		37	116	38		
Crude OR	Referent	1.2 (0.90, 1.6)	1.7 (1.1, 2.6)		Referent	0.89 (0.59, 1.3)	0.71 (0.44, 1.2)		
Adjusted OR (95% CI)[b]	Referent	1.6 (1.0, 2.4)	2.4 (1.3, 4.4)	0.0033	Referent	1.2 (0.68, 2.1)	0.94 (0.47, 1.9)	0.7582	0.0119
AAVDs									
Cases (N)	30	66	16		10	54	11		
Crude OR	Referent	1.2 (0.80, 1.9)	1.7 (0.91, 3.2)		Referent	1.5 (0.76, 3.1)	0.76 (0.32, 1.8)		
Adjusted OR (95% CI)[b]	Referent	1.8 (0.97, 3.3)	2.6 (1.1, 6.1)	0.0276	Referent	1.3 (0.52, 3.4)	0.73 (0.23, 2.3)	0.4547	0.1592
PAVD									
Cases (N)	30	63	13		13	43	16		
Crude OR	Referent	1.2 (0.74, 1.8)	1.4 (0.71, 2.7)		Referent	0.94 (0.49, 1.8)	0.85 (0.4, 1.8)		
Adjusted OR (95% CI)[b]	Referent	1.2 (0.61, 2.2)	1.5 (0.62, 3.9)	0.3650	Referent	1.8 (0.76. 4.2)	1.7 (0.59, 4.7)	0.3562	0.3958
CTD									
Cases (N)	18	43	11		16	31	13		
Crude OR	Referent	1.3 (0.76, 2.3)	2.0 (0.91, 4.2)		Referent	0.55 (0.29, 1.0)	0.56 (0.26, 1.2)		
Adjusted OR (95% CI)[b]	Referent	2.1 (0.96, 4.5)	4.0 (1.4, 12)	0.0108	Referent	1.0 (0.41, 2.5)	0.91 (0.30, 2.8)	0.8555	0.0238
TVD									
Cases (N)	6	16	< 5		< 5	< 5	< 5		
Crude OR	Referent	1.5 (0.57, 3.8)	2.1 (0.59, 7.7)		Referent	NC	NC	NC	
Adjusted OR (95% CI)[b]	Referent	3.4 (0.95, 12)	4.6 (0.81, 27)	0.0846	Referent	NC	NC	NC	0.0437

AAVD = Aortic artery and valve defects, CHD = congenital heart defects, CTD = conotruncal defects, IA-IDW = intensity adjusted inverse distance weighted well count, N = number, O&G = oil and natural gas, NC = Not calculated because low counts result in unstable estimates, PAVD = Pulmonary artery and valve defects, TVD = tricuspid valve defects.

[a] Low = 0 to < 1 intensity wells per square mile; medium = 1 to < 403 intensity wells per square mile, high = ≥403 intensity wells per square mile.

[b] Adjusted for IDW count of oil and gas facilities other than wells in 10-mile buffer, IA-IDW count of air pollution sources not associated with O&G activities in 10-mile buffer, maternal age, and SES group, as well as infant parity and sex.

[c] Trend tests performed by treating categorical inverse-distance well count as an ordinal.

Table 5
Association between intensity adjusted O&G well site activity within ten-mile radius of maternal residence in second month of pregnancy and congenital heart defects for cases and controls born between 2005 and 2011 in Colorado counties with 20 or more O&G well starts per 10,000: births stratified by tertile of IA-IDW count for air pollution sources not associated with O&G activities.

	Low other air pollution sources[a]			Medium other air pollution sources[a]			High other air pollution sources[a]		
	Low[b]	Medium[b]	High[b]	Low[b]	Medium[b]	High[b]	Low[b]	Medium[b]	High[b]
Controls (N)	346	530	76	213	588	147	197	546	215
Any CHD									
Cases (N)	56	84	14	35	95	27	20	99	36
Crude OR	Ref	0.99 (0.69, 1.4)	1.2 (0.61, 2.2)	Ref	0.98 (0.65, 1.5)	1.1 (0.65, 1.9)	Ref	1.8 (1.1, 3.0)	1.6 (0.92, 2.9)
Adjusted OR (95% CI)[c]	Ref	1.2 (0.69, 2.1)	1.8 (0.73, 4.3)	Ref	1.3 (0.69, 2.4)	1.7 (0.73, 3.8)	Ref	2.4 (1.3, 4.5)	2.5 (1.2, 5.4)
AAVDs									
Cases (N)	23	38	7	11	40	9	6	42	11
Crude OR	Ref	1.1 (0.63, 1.8)	1.4 (0.57, 3.3)	Ref	1.3 (0.66, 2.6)	1.2 (0.48, 2.9)	Ref	2.5 (1.1, 6.0)	1.7 (0.61, 4.6)
Adjusted OR (95% CI)[c]	Ref	1.1 (0.48, 2.3)	1.6 (0.46, 5.3)	Ref	1.2 (0.43, 3.4)	1.3 (0.33, 4.8)	Ref	4.4 (1.6, 12)	3.5 (1.0, 12)
PAVD									
Cases (N)	20	27	< 5	14	39	10	10	41	16
Crude OR	Ref	0.92 (0.51, 1.7)	0.72 (0.21, 2.5)	Ref	1.0 (0.54, 1.9)	1.0 (0.45, 2.4)	Ref	1.5 (0.73, 3.0)	1.5 (0.65, 3.3)
Adjusted OR (95% CI)[c]	Ref	1.4 (0.55, 3.6)	1.6 (0.31, 8.2)	Ref	1.4 (0.56, 3.6)	1.9 (0.55, 6.4)	Ref	2.1 (0.91, 5.0)	2.4 (0.84, 6.8)
CTD									
Cases (N)	14	23	< 5	14	23	8	6	28	12
Crude OR	Ref	1.0 (0.53, 2.1)	1.3 (0.41, 4.0)	Ref	0.60 (0.30, 1.2)	0.83 (0.34, 2.0)	Ref	1.7 (0.69, 4.1)	1.8 (0.68, 5.0)
Adjusted OR (95% CI)[c]	Ref	1.5 (0.55, 4.2)	2.7 (0.54, 13)	Ref	1.1 (0.40, 3.2)	2.0 (0.48, 8.0)	Ref	2.5 (0.88, 7.1)	3.5 (0.97, 13)

AAVD = Aortic artery and valve defects, CHD = congenital heart defects, CTD = conotruncal defects, IA-IDW = intensity adjusted inverse distance weighted well count, IDW = inverse distance weighted count, N = number, O&G = oil and natural gas, PAVD = Pulmonary artery and valve defects, Ref = referent, TVD = tricuspid valve defects.

[a] Low = 0 to < 4.14 intensity air pollution sources per square mile; medium = 4.14 to < 8.18 intensity air pollution sources per square mile, high = ≥ 8.18 air pollution sources wells per square mile.

[b] Low = 0 to < 1 intensity wells per square mile; medium = 1 to < 403 intensity wells per square mile, high = ≥ 403 intensity wells per square mile.

[c] Adjusted for IDW count of oil and gas facilities other than wells in 10-mile buffer, IA-IDW count of air pollution sources not associated with O&G activities in 10-mile buffer, maternal age, and SES group, as well as infant parity and sex.

cellular division during cardiac neural crest formation, an acute environmental exposure during cardiac neural crest formation could induce teratogenesis (Linask, 2013;). The air pollutants emitted from O&G operations have been associated with increased oxidative stress in animal models and humans (Amin et al., 2018; Ferguson et al., 2017; Sun et al., 2012, 2018). While it is plausible that an acute maternal exposure to one or more these stressors during embryonic cardiac neural crest formation could initiate a CHD, further study will be necessary to elucidate this biological mechanism.

Our study benefited from our selection of cases and controls from the same population. Because our cohort included all births in Colorado counties with O&G activities, it is representative of Colorado's population in these areas. Using our IA-IDW model, we were able to estimate the individual level of relative O&G well activity around the mother of each case and control. In addition to SES, density of O&G facilities other than wells, and intensity of air pollution sources not associated with O&G activities, we considered other potentially important confounders (maternal age, smoking, ethnicity, and residence in a rural area as well as infant sex and infant parity) in our study design. Because adjustment for birth year did not change our results, it is unlikely that changes in Colorado's population during the study period would affect our results.

The use of the LexisNexis® database to determine maternal residence during critical periods for development of CHDs is an improvement on previous studies, but it is not without limitations. Young, non-married, and Hispanic mothers were less likely to be found in the LexisNexis® database. The sensitivity analysis of births to mother's with an address found in the second gestational month indicates that this had minimal effect on our results. Similarly, accounting for the density of other O&G facilities and intensity of air pollution sources not associated with O&G activities is an improvement on previous studies, but limitations remain. Small scale fixed air pollution sources, such as gasoline stations, and mobile air pollution sources were not included in our analysis. This may be obscuring our ability to observe associations in urban areas, such as Greeley CO, where these air pollution sources are more prevalent than in rural areas.

Our evaluation with zero wells in the 10-mile buffer as the referent and grouped IA-IDW > 0 into tertiles (see Supplemental Table 8) indicates that our choice of cut-points based on the multi-modal distribution of the IA-IDW well may have introduced some bias. However, we note that defining the referent group as IA-IDW equal to zero, results in a smaller referent group and loss of precision. Additionally, assigning cut-points based tertiles rather than the multi-modal distribution masks the effects of the highly exposed group indicated in Supplemental Fig. 1.

There also are limitations inherent to our study design and nature of the available data. CHDs remain undercounted, because data on non-live births, terminated pregnancies, and later life diagnoses (after age 3 years) is not available. Data on covariates were limited to information on the birth certificates and thus we were not able to adjust for maternal health and nutrition that may have resulted in residual confounding of unknown bias. A recent study suggests that methionine intake may modify the effect of maternal NO_2 exposures during pregnancy and CHD outcomes in offspring (Stingone et al., 2017) and offspring of mothers with pre-pregnancy diabetes are at a higher risk for CHDs (Correa et al., 2008). We were not able to account for the mother's time away from her residence, such as work and recreation, which may have led to exposure misclassification. This potential exposure error likely does not differ by cases/control status and thus has the potential to attenuate the reported results towards the null.

Our IA-IDW model estimated the average monthly intensities of O&G well site activities around the maternal residence, which may have obscured acute events on a shorter time scale (e.g. one-day). A recent study indicates that the developmental exposure window of concern could be as short as one day (Warren et al., 2016). Our inability to capture and evaluate short-time scale acute exposures may have attenuated the reported results towards the null. The small number of CTD

and TVD cases and in the stratified analyses for all CHD types led to wide confidence intervals and further attenuation towards the null.

5. Conclusion

This study provides further evidence of a positive association between maternal proximity to O&G well site activities and several types of CHDs, particularly in rural areas and in areas with high densities of air pollution sources not associated with O&G activity. At least 17 million people in the U.S and 6% of Colorado's population live within 1 mile of an active O&G well site. Taken together, our results and expanding development of O&G well sites underscore the importance of continuing to conduct comprehensive and rigorous research on the health consequences of early life exposures to O&G activities.

Declaration of Competing Interest

The authors declare they have no competing financial interests.

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Appendix A. Supplementary data

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