Environmental Pollution 202 (2015) 1–6

Contents lists available at ScienceDirect

Environmental Pollution

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

An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas

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ARTICLE INFO

Article history:
Received 6 October 2014
Received in revised form
2 March 2015
Accepted 5 March 2015
Available online 14 March 2015

Keywords:
Air pollution
Ozone
Particulate matter
Birth defects

ABSTRACT

We performed an exploratory analysis of ozone (O_3) and fine particulate matter ($PM_{2.5}$) concentrations during early pregnancy and multiple types of birth defects. Data on births were obtained from the Texas Birth Defects Registry (TBDR) and the National Birth Defects Prevention Study (NBDPS) in Texas. Air pollution concentrations were previously determined by combining modeled air pollution concentrations with air monitoring data. The analysis generated hypotheses for future, confirmatory studies; although many of the observed associations were null. The hypotheses are provided by an observed association between O_3 and craniosynostosis and inverse associations between $PM_{2.5}$ and septal and obstructive heart defects in the TBDR. Associations with $PM_{2.5}$ for septal heart defects and ventricular outflow tract obstructions were null using the NBDPS. Both the TBDR and the NBPDS had inverse associations between O_3 and septal heart defects. Further research to confirm the observed associations is warranted.

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1. Introduction

Ozone (O_3) and particulate matter (PM), two of the criteria air pollutants regulated by the Clean Air Act, have been investigated for increasing the risk of several birth outcomes, including preterm birth, low birthweight, and birth defects (US EPA, 2009, 2013). Some of those previous studies have investigated associations between birth defects and air quality in Texas. One study reported an association between increased PM_{10} concentrations and higher odds of certain cardiovascular defects (Gilboa et al., 2005). Living in census tracts with higher levels of modeled environmental exposure to benzene, estimated using the EPA Assessment System for Population Exposure Nationwide (ASPEN), was associated with greater risk of having offspring with spina bifida (Lupo et al., 2011) but not oral clefts (Ramakrishnan et al., 2013). Close residence near Toxic Release Inventory sites was associated with increased odds of oral clefts, neural tube defects, and chromosomal abnormalities (Brender et al., 2006, 2008; Suarez et al., 2007), particularly in infants of older women. There was no association with conotruncal heart defects (Langlois et al., 2009).

The goal of the current study was to perform an exploratory analysis examining broad groups of birth defects to assess the potential for associations with O_3 and fine particulate matter ($PM_{2.5}$) concentrations. Most studies of this nature utilize data from air monitors, limiting the women included in the studies to those living near monitors, which are mostly urban areas (Gilboa et al., 2005). However, in the current study, all participants residing in the study area were included; a Bayesian hierarchical model that combined modeled air pollution concentrations with air monitoring data to create bias-corrected concentrations across Texas provides information on concentrations of $PM_{2.5}$ and O_3 regardless of proximity to an air monitor. Evaluation for possible associations with birth defects was performed utilizing two study populations,

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http://dx.doi.org/10.1016/j.envpol.2015.03.001
0269-7491/© 2015 Published by Elsevier Ltd.

the Texas Birth Defects Registry (TBDR) and Texas data from the National Birth Defects Prevention Study (NBDPS). Utilizing two study populations allowed us to compare results and look for similar patterns across the studies. The TBDR covers the entire state resulting in a wide variety of exposure and a large sample size, which afforded the opportunity to investigate multiple defects. Although the NBDPS is smaller in size, limiting the number of defects able to analyzed compared to the TBDR, there is more information on maternal covariates that may add insight into whether the TBDR is biased by not including these covariates.

2. Materials and methods

2.1. Data from the Texas Birth Defects Registry

The TBDR is a population-based active surveillance system that includes the entire state of Texas (Miller, 2006). Staff visit hospitals, birthing centers, and midwives throughout Texas and identify children or pregnancies with birth defects diagnosed prenatally or up to one year after delivery. Mothers must be a resident in Texas at the time of delivery. The data from medical charts are abstracted and entered into a web-based system where they undergo extensive quality control. These data are then linked to vital records (birth, fetal death, and death certificate data).

For the current study, cases with one or more of a range of defects were obtained from this registry for singleton live births with a delivery date between 2002 and 2006. Individuals with more than one birth defect were included in all the appropriate birth defect groupings. Live-born controls from the same time period were obtained from Texas birth certificate data, and any children with birth defects were excluded.

2.2. Data from the National Birth Defects Prevention Study

A second analysis utilized data from the NBDPS, a population-based case-control study taking place in ten states. Case mothers were selected from active surveillance birth defects registries, and had given birth to a child affected by one or more of 30 birth defects selected for the study. Case records were submitted to in-depth clinical review by clinical geneticists affiliated with the NBDPS. Control mothers had given birth to a child unaffected by birth defects, and were selected from birth certificates or from hospitals in the same area and time period from which cases were drawn. Case and control mothers were invited to participate in a computer-assisted telephone interview which included questions about pregnancy and medical history, diet, lifestyle, occupational exposures, medication use, and where they lived from three months before conception of the index child through the date of delivery. The interview was conducted with women whose infants are between 6 weeks and 2 years of age. More details on the NBDPS can be found elsewhere (Yoon et al., 2001).

For the current study, only women from the Texas enrollment site were included. Because of protocol limitations on participating states, the Texas NBDPS area included only 10–20% of Texas births in any year.

2.3. Exposure data

A hierarchical Bayesian model that combined data from air monitors (provided by the US EPA Air Quality System) with modeled air pollution estimates from the US EPA's Community Multiscale Air Quality (CMAQ) model (which bases its estimates on data from EPA's National Emissions Inventory and meteorological and geographical factors) estimated ambient air concentrations (McMillan et al., 2010). This combination made use of air monitoring data but also provided estimates of air pollutant concentrations for areas where no monitoring data was available. The estimates covered the entire spatial extent of Texas in the form of grid cells (12 km $\times$ 12 km) (data available for download here: http://www.epa.gov/esd/land-sci/lcb/lcb_fdaqs_archive.html). For the TBDR, residence at birth was extracted from birth certificates for both cases and controls and geocoded using ARCGIS by the Texas Department of State Health Services. The NBDPS database contained information on all residences during pregnancy, which was geocoded by the Agency for Toxic Substance and Disease Registry at CDC. In the NBDPS data, slightly less than 20% of women moved during the first trimester. To calculate the air pollution concentrations for these women, the air pollution concentrations at each woman's residential address were summed for the time period the woman resided there, and this sum was divided by 90, the number of days in the first trimester.

Each geocoded address was matched to the appropriate CMAQ grid cell. The daily estimates for 24-hour average $PM_{2.5}$ concentrations and 8-hour maximum O_3 concentrations provided by the CMAQ model were then averaged across the first trimester using the grid cell for reported maternal residence to create mean concentration values. A total of 90.2% of the cases and 91.5% of the controls in the TBDR were able to be geocoded and included in the study. Of the addresses provided in the NBDPS, 94.0% were geocoded and assigned a grid cell.

2.4. Statistical analyses

Associations between air pollutant concentrations and birth defects were examined using logistic regression, including both crude and adjusted single-pollutant models. Analysis was limited to birth defects with N $\geq$ 50. A Bonferroni multiple comparisons adjustment was performed and reflected in the confidence intervals of the estimates of the TBDR analyses. Due to small numbers for most defects, only a few of the NBDPS birth defects were examined and multiple comparison adjustments were not used. Covariates included in the adjusted analyses were chosen based on those previously reported in the literature and variables thought to be associated with both the exposure and outcome but not on the causal pathway. These included: prenatal care in the first trimester (yes, no), number of previous live births (first birth, second birth, third or greater birth), maternal age (5-year age categories), maternal educational attainment (less than high school degree, high school degree, more than a high school degree), and maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic other). The TBDR also included a variable for urbanicity (determined using 2003 rural-urban continuum codes (RUCC) assigned based on county; metropolitan urbanized counties [RUCC: 1–3], nonmetropolitan urbanized [RUCC: 4, 5], less urbanized or thinly populated [RUCC: 6–9]) (data available for download here: www.ers.usda.gov/data-products/rural-urban-continuum-codes/.aspx). No covariates were missing more than 5% of their values. Multiple imputation was performed in the TBDR analysis to estimate the values for any missing data on covariates. Information on additional covariates, such as behaviors taking place during the month before pregnancy through the first trimester (i.e., folic acid/multivitamin use, alcohol consumption, and smoking), was available in the NBDPS and used in further adjusted analyses for this study. In addition, co-pollutant analyses that included both the estimated O_3 and $PM_{2.5}$ concentrations, as well as the covariates listed for the adjusted analyses, were performed for both the TBDR and the NBDPS.

This study has been approved by Institutional Review Boards at the Texas Department of State Health Services and the University of North Carolina at Chapel Hill.

3. Results

Descriptive characteristics of the women included in the analysis of the TBDR are listed in Table 1. There were approximately 21,000 cases with any type of birth defect and 1.4 million births without birth defects. The majority of women had at least one previous birth and had at least a high school degree. Slightly less than 50% of women were between the ages of 25–34 years. Most women lived in metropolitan areas.

Estimated concentrations of $PM_{2.5}$ and O_3 were similar for cases and controls (Table 2). The mean $PM_{2.5}$ concentration was approximately 12 $\mu g/m^3$and the mean O_3 concentration was about 40 ppb.

The exploratory analysis of the Registry and vital records data for 2002–2006 produced many null findings between the air pollutants and most birth defects (Table 3). Statistically significant inverse associations were observed between $PM_{2.5}$ and septal heart defects and obstructive heart defects in adjusted and/or co-pollutant models. No positive associations were observed between $PM_{2.5}$ concentrations and birth defects. Similar to $PM_{2.5}$, an inverse relationship was observed between O_3 concentration and septal heart defects. Additionally, higher O_3 concentrations were associated with increased risk of craniosynostosis in adjusted and co-pollutant models.

For the examination of the NBDPS Texas data for 2002–2006, our analysis was limited to three birth defects: septal heart defects (n = 349), ventricular outflow tract obstruction defects (n = 84), and oral clefts (n = 95). The majority of women in the NBDPS from Texas were aged 20–29 years and over 70% of women were Hispanic. Approximately 87% of women received prenatal care in the first trimester and close to 80% stated they used folic acid supplements/multivitamins during the month prior to conception through three months post-conception (Table 1). The average concentration estimates for the women varied from that of the TBDR, most notably with lower $PM_{2.5}$ concentrations (Table 2). No associations were observed between $PM_{2.5}$ concentration and septal heart defects, ventricular outflow tract obstruction, or oral clefts (Table 4). A weak inverse association was present between O_3 concentration and septal heart defects. No associations were observed between O_3 concentrations and the other two defects examined. The results were robust to adjustment for the other pollutant and additional covariates (folic acid/multivitamin use, alcohol consumption, and smoking).

Table 1
Descriptive characteristics of women studied from the TBDR and the NBDPS.

	TBDR						NBDPS					
	Cases (N = 21,060)		Controls[a] (N = 1,401,611)		Total (N = 1,422,671)		Cases (N = 291)		Controls (N = 521)		Total (N = 812)	
	N	%	N	%	N	%	N	%	N	%	N	%
Received prenatal care in first trimester												
No	2820	13.98	175,120	12.95	177,940	12.96	41	14.09	61	11.71	102	12.56
Yes	17,358	86.02	1,177,539	87.05	1,194,897	87.04	250	85.91	460	88.29	710	87.44
Number of previous live births												
0 births	8355	40.48	534,759	38.87	543,114	38.89	106	36.43	189	36.28	295	36.33
1 birth	6149	29.79	433,344	31.50	439,493	31.47	83	28.52	171	32.82	254	31.28
2 + births	6138	29.74	407,784	29.64	413,922	29.64	102	35.05	161	30.90	263	32.39
Maternal age												
<20	2918	13.86	191,177	13.64	194,095	13.64	60	20.62	91	17.47	151	18.60
20–24	5860	27.83	395,657	28.23	401,517	28.22	90	30.93	149	28.60	239	29.43
25–29	5454	25.90	374,001	26.68	379,455	26.67	76	26.12	131	25.14	207	25.49
30–34	4192	19.91	287,377	20.50	291,569	20.50	49	16.84	110	21.11	159	19.58
35–39	2135	10.14	126,967	9.06	129,102	9.08	15	5.15	30	5.76	45	5.54
≥40	501	2.38	26,366	1.88	26,867	1.89	1	0.34	10	1.92	11	1.35
Maternal race/ethnicity												
Non-hispanic white	7400	35.18	492,888	35.21	500,288	35.21	58	20.00	131	25.29	189	23.39
Non-hispanic black	2173	10.33	159,787	11.41	161,960	11.40	2	0.69	7	1.35	9	1.11
Hispanic	10,770	51.20	690,521	49.32	701,291	49.35	222	76.55	365	70.46	587	72.65
Non-hispanic other	693	3.29	56,772	4.06	57,465	4.04	8	2.76	15	2.90	23	2.85
Maternal highest level of education												
Less than a high school degree	6874	32.87	439,266	31.59	446,140	31.60	94	32.30	147	28.27	241	29.72
High school degree	6149	29.40	398,070	28.62	404,219	28.63	85	29.21	157	30.19	242	29.84
More than a high school degree	7890	37.73	553,680	39.80	561,570	39.77	112	38.49	216	41.54	328	40.44
Urbanicity												
Metropolitan, urbanized	19,299	91.64	1,276,813	91.10	1,296,112	91.10						
Not metropolitan, urbanized	683	3.24	50,100	3.57	50,783	3.57						
Less urbanized or thinly populated	1078	5.12	74,698	5.33	75,776	5.33						
Maternal consumption of folic acid/multivitamin during the month prior to conception through three months post-conception												
No							56	19.24	111	21.31	167	20.57
Yes							235	80.76	410	78.69	645	79.43
Maternal smoking present during the month prior to conception through three months post-conception												
No							253	86.94	424	81.54	677	83.48
Yes							38	13.06	96	18.46	134	16.52
Maternal alcohol consumption during the month prior to conception through three months post-conception												
No							225	77.59	364	70.00	589	72.72
Yes							65	22.41	156	30.00	221	27.28

Information was missing for the following variables: TBDR - prenatal care (n = 49,834), number of previous live births (n = 26,142), maternal age (n = 66), maternal race/ethnicity (n = 1667), and maternal education (n = 10,742). The percentage of missing values was similar for cases and controls; NBDPS - maternal race/ethnicity (n = 4), maternal education (n = 1), maternal smoking (n = 1), maternal alcohol consumption (n = 2).

[a] Controls used in the analysis for the TBDR were obtained from vital records.

Table 2
Air pollution concentrations estimated using the CMAQ models for the first trimester of pregnancy.

	Cases	Controls	Total
Air pollutant concentrations for the TBDR			
$PM_{2.5}$ concentration ($\mu g/m^3$)			
Mean (SD)	11.6 (3.8)	12.1 (3.8)	12.1 (3.8)
Median	11.6	12.0	12.0
IQR	8.8–14.0	9.4–14.4	9.4–14.4
Range	2.9–26.9	2.2–26.9	2.2–26.9
O_3 concentration (ppb)			
Mean (SD)	40.0 (8.8)	40.3 (8.5)	40.3 (8.5)
Median	39.8	40.5	40.5
IQR	32.7–46.7	33.4–46.8	33.4–46.8
Range	18.5–64.6	18.2–65.1	18.2–65.1
Air pollutant concentrations for the NBDPS			
$PM_{2.5}$ concentration ($\mu g/m^3$)			
Mean (SD)	8.2 (2.5)	8.3 (2.5)	8.2 (2.5)
Median	7.9	7.8	7.9
IQR	6.4–9.5	6.7–9.6	6.5–9.5
Range	3.2–21.3	3.7–20.2	3.2–21.3
O_3 concentration (ppb)			
Mean (SD)	37.0 (9.0)	37.7 (9.6)	37.2 (9.2)
Median	34.8	35.0	34.9
IQR	30.1–42.4	29.8–47.0	30.0–43.4
Range	22.6–62.3	22.1–59.8	22.1–62.3

SD: standard deviation; IQR: interquartile range.

4. Discussion

This study examined two different datasets to perform an exploratory analysis examining the potential associations between $PM_{2.5}$ and O_3 concentrations and various birth defects, which allowed examination of both a large number of defects (TBDR) and additional confounders (NBDPS), as well as looking for similarities across the results from each dataset. Many birth defects not previously examined were included in this study. Null associations were produced for the majority of defects. However, a few associations in either direction were observed.

Higher O_3 concentrations were associated with increased odds of craniosynostosis. Conversely, higher $PM_{2.5}$ concentrations were associated with decreased odds of craniosynostosis. To our knowledge, no other studies have reported on the relationship between O_3 or $PM_{2.5}$ concentrations and craniosynostosis. It is possible that these associations arose by chance alone; however, we employed the Bonferroni correction to preserve the rate of false positive findings at 5%. Thus, this is an area of research that deserves additional follow-up.

The analyses of both datasets estimated an inverse association between O_3 concentration and septal heart defects. Multiple studies have been conducted examining the association between O_3 concentration and various heart defects. An earlier study performed in Texas also reported an inverse association between O_3 concentration and ventricular septal defects and null associations between O_3 concentrations and other cardiovascular defects (Gilboa et al., 2005). In other studies, many septal and other heart defects have not suggested an association, positively or negatively, with O_3 concentrations (Agay-Shay et al., 2013; Dadvand et al., 2011; Hansen et al., 2009; Padula et al., 2013a; Ritz et al., 2002; Stingone et al., 2014; Strickland et al., 2009; Vinikoor-Imler et al., 2013); certain birth defects showed associations with O_3 concentrations in a couple studies, but the specific cardiovascular defects varied by study (Dadvand et al., 2011; Hansen et al., 2009; Vinikoor-Imler et al., 2013).

Increased $PM_{2.5}$ concentrations were associated with lower odds of septal heart defects and obstructive heart defects in the TBDR, but these associations were null in the analyses using NBDPS data. Other studies have also reported inverse associations between $PM_{2.5}$ and various septal defects (Padula et al., 2013a; Schembari

Table 3
Odds ratios [95% confidence intervals][a] for the associations between $PM_{2.5}$ and O_3 concentrations[b] during the first trimester and birth defects[c] in single and co-pollutant models using the TBDR data.

	N for each defect	$PM_{2.5}$			O_3		
		Single pollutant models		Co-pollutant Models	Single pollutant models		Co-pollutant models
		Crude	Adjusted[d]	Adjusted[d]	Crude	Adjusted[d]	Adjusted[d]
Anencephaly/Craniorachischisis	84	1.03 [0.64, 1.64]	1.03 [0.62, 1.69]	1.03 [0.61, 1.74]	0.94 [0.55, 1.63]	0.99 [0.57, 1.72]	0.98 [0.55, 1.75]
Spina bifida	447	0.88 [0.71, 1.08]	0.92 [0.74, 1.14]	0.92 [0.73, 1.15]	0.95 [0.75, 1.20]	0.98 [0.77, 1.25]	1.01 [0.79, 1.30]
Hydrocephalus	671	0.95 [0.81, 1.13]	0.93 [0.78, 1.12]	0.92 [0.76, 1.11]	1.02 [0.84, 1.24]	1.03 [0.85, 1.26]	1.06 [0.87, 1.30]
Anotia or microtia	387	0.90 [0.72, 1.12]	0.93 [0.73, 1.17]	0.87 [0.68, 1.11]	1.13 [0.87, 1.45]	1.23 [0.95, 1.59]	1.29 [0.99, 1.68]
Conotruncal heart defects	1379	1.00 [0.89, 1.12]	0.98 [0.87, 1.11]	0.99 [0.86, 1.12]	0.97 [0.85, 1.12]	0.98 [0.86, 1.12]	0.99 [0.85, 1.14]
Septal heart defects	14,577	**0.82 [0.79, 0.85]**	**0.79 [0.75, 0.82]**	**0.79 [0.76, 0.83]**	**0.88 [0.84, 0.92]**	**0.89 [0.85, 0.93]**	**0.96 [0.92, 1.00]**
Atrioventricular septal defects	361	0.90 [0.72, 1.13]	0.92 [0.72, 1.17]	0.93 [0.71, 1.20]	0.95 [0.73, 1.23]	0.94 [0.72, 1.24]	0.97 [0.73, 1.28]
Obstructive heart defects	2226	**0.90 [0.82, 0.98]**	**0.88 [0.79, 0.97]**	**0.88 [0.79, 0.98]**	0.96 [0.87, 1.07]	0.95 [0.85, 1.06]	0.99 [0.89, 1.11]
Anomalous pulmonary venous return	271	0.93 [0.71, 1.21]	1.00 [0.76, 1.32]	1.00 [0.74, 1.34]	0.97 [0.71, 1.31]	1.01 [0.74, 1.38]	1.01 [0.73, 1.40]
Oral clefts	2003	**0.90 [0.82, 0.99]**	0.95 [0.85, 1.05]	0.93 [0.83, 1.03]	1.08 [0.96, 1.20]	1.06 [0.94, 1.19]	1.08 [0.96, 1.22]
Esophageal atresia	205	1.10 [0.82, 1.48]	1.01 [0.73, 1.39]	1.03 [0.74, 1.44]	0.94 [0.66, 1.34]	0.94 [0.66, 1.34]	0.93 [0.64, 1.35]
Intestinal atresia/Stenosis	982	0.91 [0.79, 1.04]	0.90 [0.77, 1.04]	0.88 [0.76, 1.03]	1.01 [0.86, 1.19]	1.02 [0.87, 1.20]	1.06 [0.90, 1.26]
Biliary atresia	110	0.78 [0.51, 1.19]	0.75 [0.47, 1.19]	0.69 [0.43, 1.12]	1.18 [0.73, 1.91]	1.20 [0.74, 1.94]	1.33 [0.81, 2.20]
Hypospadias[e]	369	1.21 [0.97, 1.51]	1.14 [0.89, 1.44]	1.09 [0.85, 1.40]	1.29 [0.99, 1.68]	1.20 [0.92, 1.57]	1.17 [0.89, 1.55]
Longitudinal limb deficiency defects	261	0.83 [0.63, 1.09]	0.80 [0.60, 1.07]	0.79 [0.58, 1.07]	0.98 [0.72, 1.34]	0.97 [0.71, 1.33]	1.05 [0.75, 1.45]
Transverse limb deficiency defects	393	0.86 [0.69, 1.07]	0.89 [0.70, 1.13]	0.87 [0.68, 1.12]	1.06 [0.82, 1.36]	1.04 [0.80, 1.35]	1.09 [0.83, 1.42]
Craniosynostosis	585	0.85 [0.71, 1.02]	0.85 [0.70, 1.04]	**0.78 [0.64, 0.96]**	**1.28 [1.04, 1.58]**	**1.28 [1.04, 1.58]**	**1.38 [1.11, 1.72]**
Diaphragmatic hernia	336	1.04 [0.82, 1.31]	1.03 [0.80, 1.32]	1.00 [0.77, 1.30]	1.09 [0.83, 1.43]	1.10 [0.83, 1.45]	1.10 [0.82, 1.46]
Omphalocele	179	0.98 [0.71, 1.35]	0.94 [0.66, 1.33]	0.97 [0.67, 1.40]	0.88 [0.60, 1.28]	0.88 [0.60, 1.28]	0.88 [0.59, 1.32]
Gastroschisis	652	**0.79 [0.67, 0.94]**	0.89 [0.75, 1.07]	0.87 [0.72, 1.05]	1.06 [0.87, 1.29]	1.07 [0.87, 1.30]	1.11 [0.90, 1.37]

Results in bold are those that are considered statistically significant.
[a] Confidence intervals reflect a Bonferroni multiple comparison adjustment.
[b] ORs are per 1 change in the IQR of each pollutant (13.3 ppb for O_3 and 5.0 $\mu g/m^3$ for $PM_{2.5}$).
[c] Birth defects are listed in order of ICD-9 code.
[d] Adjusted for receiving prenatal care during the first trimester, number of previous live births, maternal age, maternal race/ethnicity, maternal education, and urbanicity.
[e] For Hypospadias, Controls N = 711,833; For all other outcomes, Controls N = 1,401,611.

Table 4
Odds ratios (95% confidence intervals) for the associations between $PM_{2.5}$ and O_3 concentrations[a] during the first trimester and birth defects in single and co-pollutant models using the NBDPS data.

	N for each defect	$PM_{2.5}$				O_3			
		Single pollutant models			Co-pollutant models	Single pollutant models			Co-pollutant models
		Crude	Adjusted[b]	Adjusted[c]	Adjusted[b]	Crude	Adjusted[b]	Adjusted[c]	Adjusted[b]
Septal heart defects	349	0.98 [0.81, 1.17]	0.99 [0.82, 1.20]	1.01 [0.83, 1.22]	1.03 [0.85, 1.26]	0.81 [0.64, 1.03]	**0.75 [0.58, 0.97]**	**0.73 [0.57, 0.95]**	**0.74 [0.57, 0.96]**
Ventricular outflow tract obstruction	84	0.96 [0.72, 1.28]	0.94 [0.70, 1.27]	0.95 [0.71, 1.28]	0.95 [0.71, 1.27]	0.80 [0.57, 1.14]	0.83 [0.57, 1.22]	0.82 [0.56, 1.21]	0.83 [0.57, 1.22]
Oral clefts	95	1.00 [0.76, 1.32]	1.04 [0.78, 1.39]	1.06 [0.79, 1.42]	1.04 [0.78, 1.39]	1.13 [0.82, 1.55]	0.97 [0.68, 1.39]	0.96 [0.66, 1.39]	0.96 [0.67, 1.39]

Results in bold are those that are considered statistically significant.
[a] ORs are per 1 change in the IQR of each pollutant (13.4 ppb for O_3 and 3.0 $\mu g/m^3$ for $PM_{2.5}$).
[b] Adjusted for receiving prenatal care during the first trimester, number of previous live births, maternal age, maternal race/ethnicity, and maternal education.
[c] Adjusted model plus folic acid/multivitamin use, smoking, and alcohol consumption during the month prior to conception through the first trimester.

et al., 2014; Stingone et al., 2014; Vinikoor-Imler et al., 2013), and some studies reported null associations with point estimates in the inverse direction (Agay-Shay et al., 2013; Strickland et al., 2009). An earlier study in Texas reported that higher PM concentrations were associated with higher odds of atrial septal defects, but this study utilized a larger particulate size fraction, PM_{10} (Gilboa et al., 2005). Although in some studies associations were also observed for certain cardiovascular defects (Padula et al., 2013a; Stingone et al., 2014; Strickland et al., 2009), the specific defect varied by study. As in our study, most studies report null associations between $PM_{2.5}$ and other cardiovascular defects (Dolk et al., 2010; Padula et al., 2013a; Schembari et al., 2014; Stingone et al., 2014; Strickland et al., 2009; Vinikoor-Imler et al., 2013).

The analyses of the air pollutants and oral clefts produced null findings in both the TBDR and the NBDPS datasets. This lack of association has been confirmed in previous studies. Other studies have reported null associations between oral clefts and $PM_{2.5}$ concentrations (Dolk et al., 2010; Marshall et al., 2010; Padula et al., 2013b; Schembari et al., 2014; Vinikoor-Imler et al., 2013) and O_3 concentrations (Gilboa et al., 2005; Hansen et al., 2009; Padula et al., 2013b; Ritz et al., 2002; Vinikoor-Imler et al., 2013). Two studies demonstrated associations between higher O_3 concentrations and increased odds of oral clefts (Hwang and Jaakkola, 2008; Marshall et al., 2010), but for one of the studies it was observed only when restricted to cleft palate only, and women living near an air monitor (Marshall et al., 2010).

Although not statistically significant, an increased effect estimate was observed between O_3 concentration and anotia/microtia. Similarly, a potential association was noted between O_3 concentration and anotia/microtia in a study conducted in North Carolina (Vinikoor-Imler et al., 2013). While neither study reported estimates that were statistically significant, the replication of this previously observed estimate is important and deserves further consideration and research. Conversely, the previous study also demonstrated a potential association between $PM_{2.5}$ concentrations and anotia/microtia that was not observed in the current study, which had point estimates for that relationship in an inverse direction.

This study has certain limitations. While the use of CMAQ data to estimate exposures is a novel contribution which allows the inclusion of a much larger study population, the exposure data is affected by measurement error issues from a number of different sources. The first source of measurement error is that the exposure data is an indirect estimate. Another source of measurement error is that the data for the Registry study were taken from the TBDR and birth certificates, which record residence at the time of delivery. However, most birth defects occur within three months of conception, so there is potential for exposure misclassification based on residence; in Texas, 30% of case mothers and 24% of control mothers change residence between conception and delivery (Lupo et al., 2010). On the other hand, that same study found that maternal residential movement during pregnancy was generally within short distances, was typically not different between cases and controls, and did not significantly influence environmental benzene exposure assessment using the US EPA Assessment System for Population Exposure Nationwide, modeled at the census tract level. Additionally, the assignment of air pollution estimates is based on residential address. This does not take into account exposure concentrations during times away from the home, during commutes, etc. Another limitation related to exposure measurement is that we did not have information on time spent outdoors. The cases examined in both the TBDR and the NBDPS data could have had other birth defects, and thus may be somewhat etiologically heterogeneous (i.e. cases with versus cases without other birth defects). That information was not included in our exploratory study and deserves consideration in further research. This study may suffer from the problem of residual confounding by unmeasured factors. The analysis TBDR did not include variables like maternal alcohol or vitamin use, but these variables were included in the NBDPS analysis. Reassuringly, when included in the NBDPS analysis, the estimates were robust to their inclusion. In addition, O_3 concentrations are often inversely correlated with primary pollutants, such as NO_x. The inverse relationships between O_3 concentrations and some birth defects in this study may be due to positive associations that would be observed with the primary pollutants. This current study is limited by lack of information on additional pollutants. Another possible explanation for inverse relationships observed between O_3 and $PM_{2.5}$ with septal heart defects is that those defects exhibit high diagnostic variability, that is, they are likely to be diagnosed and recorded differently in different places and times due to variations in clinical practice (Langlois and Scheuerle, 2007). If clinicians who are more likely to diagnose minor heart defects also live in areas with low air pollution, an inverse association could result. Unfortunately, we do not know the relation between diagnostic variability and air pollution levels.

This study also has many strengths. The entire land area was included and the study did not have to be limited to women living near air monitors. When study populations are reduced to those living within a certain distance from an air monitor, often only urban areas are captured. Our use of the air pollution data allowed us to include all women in the study areas, including those living in rural areas. Also, our study utilized two different databases from Texas, which allowed us to compare results and look for patterns in associations. One of those, the NBDPS, had information on all

residences during the time period of interest, allowing us to better assign residential air pollution concentrations closer in time to the occurrence of the malformation, regardless of a woman's residential mobility. It also had details on additional covariates that were examined in the models. The other, the TBDR, had a large number of cases, including the spatial expanse of the entire state of Texas, which resulted in a large number of birth defects available for study. Finally, we were able to examine the associations in co-pollutant models to examine whether inclusion of $PM_{2.5}$ or O_3 confounded the associations.

5. Conclusions

In summary, this study was able to examine a variety of birth defects and explore their potential associations with air pollutants in order to generate hypotheses for future study. No associations were produced between the majority of birth defects and $PM_{2.5}$ and O_3 concentrations. One hypothesis for additional study arising from our analysis is that higher O_3 concentrations may be associated with increased odds of craniosynostosis. Further, O_3 concentrations in both the TBDR and the NBDPS suggest an inverse association with septal heart defects. $PM_{2.5}$ was estimated to be inversely associated with septal heart defects and obstructive heart defects in the TBDR but these associations were null in the NBDPS. Further research to understand the inverse association between air pollutant concentrations and septal defects, as well as, to confirm the observed association between O_3 concentrations and craniosynostosis are warranted.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA, the Centers for Disease Control and Prevention, or the Texas Department of State Health Services.

Acknowledgments

This publication was supported in part through a cooperative agreement (U01DD000494) between the Centers for Disease Control and Prevention and the Texas Department of State Health Services (DSHS). This publication was also supported in part by Title V Maternal and Child Health Block Grants Funds from the Office of Title V and Family Health, Texas DSHS.

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