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Short communication

$PM_{2.5}$ metal constituent exposure and stillbirth risk in Harris County, Texas

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ABSTRACT

There is limited evidence on the role of exposure to chemical constituents of fine particulate matter ($PM_{2.5}$) in risk for stillbirth. Thus, we conducted a case-control study in Harris County, Texas between 2008 and 2013, utilizing a 6:1 ratio of controls to individually matched cases. We linked birth and fetal death records with $PM_{2.5}$ data from a single air monitoring station and estimated maternal exposures to metal constituents of $PM_{2.5}$ over the risk period (defined by the gestational length of each case). We applied conditional logistic regression and modeled air pollutant exposures as continuous variables. We observed null associations for most metal constituents (Al, Cr, Cu, Fe, Pb, Mn, Ni, Se and Ti). However, we observed a modest increase in risk for stillbirth (adjusted odds ratio (OR) = 1.11, 95% confidence interval (CI): 1.02, 1.20) associated with a 0.007 $\mu g/m^3$ interquartile range (IQR) increase in exposure to zinc (Zn) $PM_{2.5}$. This study adds to the scarce literature evaluating associations between $PM_{2.5}$ metal constituents and stillbirth and points to the need for further research in this area.

1. Introduction

Two recent meta-analyses on the association between maternal exposure to fine particulate matter (aerodynamic diameter < 2.5 µm; $PM_{2.5}$) and stillbirth have reported elevated but not statistically significant summary risk estimates (Zhu et al., 2015; Siddika et al., 2016). Recent studies have also reported evidence of elevated risks (Mendola et al., 2017; Ebisu et al., 2018; Yang et al., 2018). The chemical variation of $PM_{2.5}$ constituents could vary by study region due to differences in the mix of air pollutant sources across locations (Symanski et al., 2014). In turn, this may explain the inconsistency of findings from investigations of the association between $PM_{2.5}$ and adverse birth outcomes (Sun et al., 2016).

The biological pathways through which specific constituents of $PM_{2.5}$ may impact stillbirth are unclear. Evidence from toxicological studies suggests that metal constituents of $PM_{2.5}$ are associated with oxidative stress, leading to DNA damage and potentially inducing systemic inflammation (Kim et al., 2004; Sørensen et al. 2005; Wei et al., 2009). Some metals may also inhibit DNA repair activity (Møller et al. 2014). Both oxidative stress and inflammation have been linked to preterm birth and low birth weight (Ferguson and Chin, 2017; Klepac et al., 2018) and these mechanisms might explain the association between $PM_{2.5}$ and stillbirth as well.

Unlike other adverse birth outcomes (low birth weight and preterm birth) (Darrow et al., 2009; Bell et al., 2010; Ebisu and Bell, 2012; Basu et al., 2014; Laurent et al., 2014), only one recently published investigation, to our knowledge, has examined the impact of $PM_{2.5}$ chemical constituents on stillbirth (Ebisu et al., 2018). Given the paucity of studies in the literature and our recent finding of exposure to heavy metals among economically disadvantaged pregnant women (Whitworth et al., 2017), we examined the association between metal constituents of $PM_{2.5}$ and stillbirth in Harris County, Texas, which includes Houston, the fourth largest city in the United States (U.S.) with a high density of industrial activity (e.g., petrochemical complexes) and heavily trafficked roadways (Sexton et al., 2007).

2. Material and methods

In a previous retrospective cohort study (Rammah et al. 2019), we obtained 1,874 fetal death records and 392,512 live birth records from the Texas Department of State Health Services (TX DSHS) for all singleton pregnancies in Harris County, Texas from January 2008 to

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December 2013. Briefly, we excluded records with missing gestational age and weight (< 1%) and live births with implausible gestational age and birth weight combinations (< 1%) (Alexander et al., 1996), as well as any record with a gestational age outside of the 20–44 week range (1.1%). To avoid fixed cohort bias (Strand et al., 2011), we further excluded women with conception dates more than 20 weeks before January 1, 2008 or less than 44 weeks before December 31, 2013, based on the shortest and longest gestational ages in the original study (7.68%). Following these exclusions, we extracted maternal and fetal characteristics from vital statistics records for 1,599 stillbirths and 324,188 full-term (≥37 weeks of gestation) live births. After excluding records with missing data (27% of stillbirths and 2% of live births) on risk factors of interest, we nested a case-control study within the entire cohort by randomly selecting six full-term controls (i.e., full-term live births) per case (i.e., stillbirth at ≥ 20 weeks of gestation). The University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects and the Texas DSHS Institutional Review Board approved this study.

We obtained chemically speciated $PM_{2.5}$ data (reported as 24-h averages in $\mu g/m^3$) from two stationary monitors located in Harris County (maintained by the Texas Commission on Environmental Quality). Data on metals were evaluated for use in the present study on the basis of completeness and the proportion of measurements above the method detection limit (MDL). We assigned exposure to each mother based on data from one station with little (5% or less) missing data over the 6-year study period and with 10% or less of the measurements below the MDL for aluminum (Al), chromium (Cr), copper (Cu), iron (Fe), lead (Pb), manganese (Mn), nickel (Ni), strontium (Sr), titanium (Ti) and zinc (Zn). We assigned measurements below the federal MDL (EPA, 2018) a value of ½ of the MDL (Hornung and Reed, 1990). For each case mother and her six linked controls, we estimated mean maternal exposures to $PM_{2.5}$ metal constituents over the risk period, defined by the gestational age of each case. For example, if the gestational period for a case mother was 25 weeks, then the exposure window for that case and her linked controls was limited to 25 weeks. We also retrieved average daily ambient temperature and dew point temperature data from seven Harris County meteorological stations. Measurements at these stations were highly correlated and we observed little difference in the mean and standard deviation between them. We therefore estimated daily average apparent temperature (reported in degrees Celsius; °C) from a single monitoring station (National Climatic Data Center, 2017). As with our exposure assessment for $PM_{2.5}$ metals, we defined the exposure period based on the gestational age of the cases.

We used conditional logistic regression to examine the association between $PM_{2.5}$ metal constituents and stillbirth. We used a continuous exposure metric and evaluated results per interquartile range (IQR) increases in exposure ($\mu g/m^3$). We adjusted for apparent temperature and several maternal risk factors that were identified *a priori* with information from birth and fetal death records: maternal age, race/ethnicity, education, smoking, pre-pregnancy body mass index (BMI) (weight (kg)/height (m^2)) and number of prenatal care visits (none, < 10 visits, ≥10 visits). All statistical analyses were conducted using SAS software (Version 9.4, SAS Institute, Cary, North Carolina).

3. Results

Selected maternal and fetal characteristics for cases and controls are presented in Table 1. Over half of all women were of Hispanic origin, had less than a high school education and were between the ages of 20 and 29. Characteristics among cases and controls were mostly similar, though 62% of cases had a BMI ≥25 kg/m^2 compared to 50% of controls. Further, non-Hispanic black women were 31% of cases and 17% of controls, and the majority of cases (81%) had fewer than 10 prenatal care visits, compared to 53% of controls. As shown in Table 2, we observed generally null associations in crude and adjusted models except for one metal constituent. An IQR increase ((0.007 $\mu g/m^3$) in Zn $PM_{2.5}$ exposure was associated with an 11% increase in the odds for stillbirth (adjusted OR = 1.11%, 95% CI: 1.02, 1.21).

Table 1
Selected maternal characteristics of cases and controls in Harris County, Texas, 2008–2013.

Characteristic	Cases	Controls	Total
	(n = 1,172)	(N = 7,032)	(N = 8,204)
	%	%	%
Maternal age (years)			
< 20	10.6	11.0	11.0
20–24	23.3	24.5	24.3
25–29	26.9	26.7	26.7
30–34	20.8	24.2	23.7
35–39	13.3	11.3	11.6
≥40	5.1	2.3	2.7
Maternal Race			
Non-Hispanic White	18.3	23.4	22.7
Non-Hispanic Black	30.5	17.4	19.3
Hispanic	46.0	51.6	50.8
Other/Unknown	5.3	7.5	7.2
Maternal Education			
High school or less	55.5	54.0	54.2
Some college	27.7	23.5	24.1
College or beyond	16.8	22.6	21.7
Prenatal Care visits			
None	2.7	3.5	3.4
< 10	81.1	53.1	57.1
≥10	16.2	43.4	39.5
Smoking			
No smoking before or during pregnancy	94.5	96.5	96.2
Smoked 3 months before and during pregnancy	5.5	3.5	3.8
Pre-pregnancy BMI (kg/m2)			
< 18.5	2.6	4.6	4.3
18.5 to 24.9	35.8	45.1	43.7
25.0 to 29.9	29.3	27.5	27.8
30.0 to 34.9	15.7	13.8	14.0
≥35	16.7	9.1	10.2

BMI = body mass index.

Table 2
Crude and Adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for the associations between interquartile range (IQR) increases in maternal exposure to $PM_{2.5}$ metal constituents and stillbirth, Harris County, Texas, 2008–2013.

Pollutant	Median	IQR	Crude Model		Adjusted Model	
			OR	95% CI	OR	95% CI
Al	0.07965	0.0912	0.99	0.89, 1.09	0.99	0.83, 1.19
Cr	0.00134	0.0004	0.99	0.91, 1.07	1.01	0.92, 1.11
Cu	0.00706	0.006	0.96	0.86, 1.08	0.93	0.83, 1.06
Fe	0.13133	0.066	0.99	0.9, 1.09	0.99	0.85, 1.16
Pb	0.00364	0.0016	0.98	0.9, 1.06	0.95	0.87, 1.03
Mn	0.00574	0.0032	1.01	0.91, 1.12	1.04	0.92, 1.16
Ni	0.00146	0.0003	0.97	0.89, 1.06	0.97	0.89, 1.07
Sr	0.00186	0.0006	0.97	0.91, 1.03	0.95	0.89, 1.02
Ti	0.00856	0.008	1.00	0.9, 1.11	1.03	0.84, 1.26
Zn	0.07965	0.0074	1.11	1.02, 1.2	1.11	1.02, 1.2

[a] Adjusted for age, race, education, number of prenatal care visits, smoking, BMI and apparent temperature.

4. Discussion

Given the paucity of studies that have examined associations between specific $PM_{2.5}$ chemical constituents and fetal death, we conducted a study among a cohort of pregnant women living in Harris County, Texas, an urban center with a high density of industries, heavily trafficked roadways and documented poor air quality (Sexton et al. 2006, 2007). In our evaluation of associations between 10 metal constituents and risk for stillbirth, we observed elevated risks for Zn only. In the only other study available for comparison, Ebisu et al. also reported elevated but lower risks for Zn (OR = 1.05, 95% CI: 1.00, 1.11 per 0.012 μg/m^3 IQR increase) (Ebisu et al., 2018). In contrast to our findings, Ebisu et al. also reported positive associations for Al, Cu, Fe, and Ti. While our exposure assessment shared similar features (e.g., estimates generated for linked controls based on the gestational age of the case), there were important differences. These included a significantly larger sampling frame that restricted the study population to pregnant women from 2002 to 2009 whose residential zip code tabulation area centroids were within 20 km of one of eight monitors operating in the state of California.

One advantage of our study is the use of a truncated risk period to assess exposure of controls that approximates the risk period of linked cases, which allowed us to account for the same potential for exposure during pregnancy between cases and controls. Yet, a limitation of our exposure assessment is that it did not capture spatial variability in outdoor air levels of $PM_{2.5}$ metals (Darrow et al., 2011; Ebisu et al., 2014) as speciated data that were deemed eligible were available from a single monitor. Further, our exposure assessment was likely more accurate for mothers living closer to the monitoring station that those living farther away. One limitation of our study was that there was more missing data on covariates (such as number of prenatal care visits) in the fetal death records as compared to birth records. As is common to many air pollution epidemiologic studies that rely on vital statistics data, another limitation was our inability to account for time-activity patterns, such as time spent outdoors, or behavioral risk factors, such as alcohol use during pregnancy. However, failing to adjust for behavioral risk factors might not impact effect estimates, as suggested by Ritz and Wilhelm (2008).

5. Conclusion

Notwithstanding the spatially limited speciated $PM_{2.5}$ data, there was evidence of increased risk associated with maternal exposures to Zn $PM_{2.5}$, although the underlying biological mechanism is not clear and we cannot rule out the role of a chance finding. Petrochemical industries in the Greater Houston Area are possible sources for metal emissions, as well as traffic-related emissions (Buzcu et al., 2003). Further, a lack of zoning in the area means that industrial sources of pollution are often dispersed and close to residential neighborhoods (Qian, 2010). Future studies, applying exposure assessment methods to better capture the spatial heterogeneity of $PM_{2.5}$ constituents, are warranted especially in large urban centers characterized by myriad and diverse sources of PM. In Houston in particular, a source appointment approach might help identify emission sources for $PM_{2.5}$ constituents with the goal of mitigating exposures in residential neighborhoods that are close in proximity to one or more sources of particle pollution.

Declarations of interest

None.

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Protection of human research subjects

This investigation received approval from The University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects and the Texas Department of State Health Services (DSHS) Institutional Review Board prior to being conducted.

CRediT authorship contribution statement

Amal Rammah: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Kristina W. Whitworth:** Methodology, Writing - review & editing, Visualization. **Inkyu Han:** Methodology, Writing - review & editing, Visualization. **Wenyaw Chan:** Methodology, Writing - review & editing, Visualization. **Elaine Symanski:** Conceptualization, Resources, Methodology, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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