Environmental Research 160 (2018) 358–364

Contents lists available at ScienceDirect

Environmental Research

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

Cause-specific stillbirth and exposure to chemical constituents and sources of fine particulate matter

Keita Ebisu[a,*], Brian Malig[a], Sina Hasheminassab[b], Constantinos Sioutas[b], Rupa Basu[a]

[a] *Office of Environmental Health Hazard Assessment, California EPA, 1515 Clay Street, 16th floor, Oakland, CA 94612, USA*
[b] *Department of Civil and Environmental Engineering, University of Southern California, 3620 South Vermont Avenue, Los Angeles, CA 90089, USA*

ARTICLE INFO

Keywords:
Air pollution
Fine particulate matter ($PM_{2.5}$)
$PM_{2.5}$ Chemical constituents
Source apportionment
Stillbirth

ABSTRACT

The stillbirth rate in the United States is relatively high, but limited evidence is available linking stillbirth with fine particulate matter ($PM_{2.5}$), its chemical constituents and sources. In this study, we explored associations between cause-specific stillbirth and prenatal exposures to those pollutants with using live birth and stillbirth records from eight California locations during 2002–2009. ICD-10 codes were used to identify cause of stillbirth from stillbirth records. $PM_{2.5}$ total mass and chemical constituents were collected from ambient monitors and $PM_{2.5}$ sources were quantified using Positive Matrix Factorization. Conditional logistic regression was applied using a nested case-control study design (N = 32,262). We found that different causes of stillbirth were associated with different $PM_{2.5}$ sources and/or chemical constituents. For stillbirths due to fetal growth, the odds ratio (OR) per interquartile range increase in gestational age-adjusted exposure to $PM_{2.5}$ total mass was 1.23 (95% confidence interval (CI): 1.06, 1.44). Similar associations were found with resuspended soil (OR = 1.25, 95% CI: 1.10, 1.42), and secondary ammonium sulfate (OR = 1.45, 95% CI: 1.18, 1.78). No associations were found between any pollutants and stillbirths caused by maternal complications. This study highlighted the importance of investigating cause-specific stillbirth and the differential toxicity levels of specific $PM_{2.5}$ sources and chemical constituents.

1. Introduction

The stillbirth rate in the United States was 5.96 per 1,000 total births in 2013 (MacDorman and Gregory, 2015), which is relatively high among developed countries (Flenady et al., 2016). The rate has remained unchanged since 2006 (MacDorman and Gregory, 2015), leaving the United States short of the Healthy People 2010 target goal of 4.1 stillbirths per 1,000 total births (Centers for Disease Control, 2010), and the rate is still higher than the goal of Healthy People 2020, which is 5.6 stillbirths per 1,000 total births (U.S. Department of Health and Human Services, 2016). The public health burden of stillbirths is serious: mothers may have long-term psychological problems following a stillbirth delivery, and increased risk of recurrent stillbirths, and the costs for health-care providers and the government are enormous (Heazell et al., 2016; Lamont et al., 2015). Scientists are encouraged to prioritize research regarding stillbirth to avoid overlooking this public health topic (Froen et al., 2016).

Several environmental factors are considered as risk factors for stillbirth (e.g., maternal smoking, secondhand smoking exposure and household use of solid fuel) (Mishra et al., 2005; Leonardi-Bee et al., 2011), and the biological mechanisms underlying the relationship between these risk factors and stillbirth can be applicable to the relationship between ambient air pollution and stillbirth (Kannan et al., 2006). Although previous studies suggest associations between ambient air pollution, particularly particulate matter with aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$), and low birth weight (Ebisu and Bell, 2012; Basu et al., 2014), research on $PM_{2.5}$ and stillbirths is scarce, and the findings are inconsistent (Green et al., 2015; Faiz et al., 2013). While two systematic literature reviews evaluated the relationship between $PM_{2.5}$ and stillbirth, both concluded that there was no evidence of $PM_{2.5}$ effects on stillbirth. They, however, acknowledged that the number of studies is insufficient (Siddika et al., 2016; Zhu et al., 2015).

$PM_{2.5}$ is a mixture of many chemical constituents, which vary spatially and temporally (Bell et al., 2007). A handful of studies have

Abbreviations: Al, aluminum; NH_4^+, ammonium ion; Ca, calcium; CTM, chemical transport models; Cl, choline; CI, confidence interval; Cu, copper; EC, elemental carbon; ICD-10, International Classification of Diseases, 10th Revision; IQR, interquartile range; Fe, iron; LMP, last menstrual period; Mg, magnesium; Ni, nickel; NO_3^-, nitrate ion; OR, odds ratio; OC, organic carbon; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 µm; PMF, Positive Matrix Factorization; K, potassium; K^+, potassium ion; Si, silicon; Na, sodium; Na+, sodium ion; $SO_4^{=}$, sulfate ion; Ti, titanium; V, vanadium; Zn, zinc; ZCTA, ZIP Code Tabulation Area

* Correspondence to: 1515 Clay Street, 16th floor, Oakland, CA 94612, USA.
E-mail address: keita.ebisu@oehha.ca.gov (K. Ebisu).

http://dx.doi.org/10.1016/j.envres.2017.10.015
Received 20 July 2017; Received in revised form 5 October 2017; Accepted 7 October 2017
0013-9351/

suggested that some $PM_{2.5}$ constituents are more toxic than others (Ebisu and Bell, 2012; Basu et al., 2014; Bell et al., 2010), and this might explain some null results: less toxic $PM_{2.5}$ constituents may be present in those studies. Based on $PM_{2.5}$ chemical constituents, identifying $PM_{2.5}$ emission sources provides valuable information from a regulatory perspective. A few studies have estimated source-specific $PM_{2.5}$ levels and reported that gestational exposure to road dust (e.g., resuspension of tires debris and brake pad), secondary ammonium nitrate, secondary ammonium sulfate, and soil were associated with term low birth weight (Bell et al., 2010; Ng et al., 2017). Studies by Laurent et al. found that gasoline, diesel and commercial meat cooking were associated with term low birth weight or preterm delivery in California (Laurent et al., 2016a, 2016b). Different $PM_{2.5}$ chemical constituents and sources likely link to different health outcomes, but sufficient scientific evidence has not yet reached a consensus. The World Health Organization has called for further studies on health associated with air pollution sources (World Health Organization, 2016).

Another possible explanation for null results is that stillbirth has been treated as a single outcome. There are multiple causes of stillbirths, and each cause is likely to be associated with different risk factors (Stillbirth Collaborative Research Network Writing Group, 2011). Thus, stratifying by cause of stillbirth might be better approach than treating them as one outcome because aggregation may mask associations between certain risk factors and outcomes.

In this study, we explored whether $PM_{2.5}$ total mass, chemical constituents and sources were associated with cause-specific stillbirth in California. To the best of our knowledge, no previous studies have investigated $PM_{2.5}$ chemical constituents or sources in relation to risk of stillbirth. Identifying $PM_{2.5}$ chemical constituents and sources that are linked to increased risk of stillbirth could help decrease risk of stillbirth.

2. Materials and methods

2.1. Live birth and stillbirth data

We obtained all records of live birth and stillbirth in California from 2002/1/1 to 2009/12/31 from the California Department of Public Health. Birth-related variables were available (e.g., last menstrual period (LMP), gestational length) as well as maternal characteristics and the residential ZIP Code Tabulation Area (ZCTA) at delivery. Causes of death based on the International Classification of Diseases, 10th Revision (ICD-10), were available for stillbirth. We also obtained the percentage of households receiving subsidies from the Food Stamp Program (or Supplemental Nutrition Assistance Program) by ZCTA level from the American Community Survey. Food Stamp Program is a nutrition assistance program for low-income households in the U.S., and thus, serves as a marker for low neighborhood socio-economic status. Study protocol was approved by the California Committee for the Protection of Human Subjects.

In California, stillbirth is defined as a fetal death occurring beyond 20 weeks of gestation. Therefore, we included live births and stillbirths of gestational length between 20 and 44 weeks. We hypothesized that each cause-specific stillbirth was associated with a different risk factor, so we classified stillbirth into five categories based on ICD-10 codes: congenital malformations (Q00-Q99), fetal disorders (P19-P78), fetal growth (P05-P08), maternal complications (P00, P01, P04), and obstetric complications (P02, P03). Some causes of death did not match any of the causes listed above, and some were unspecified (P95: 'fetal death of unspecified cause'). These stillbirths (i.e. other cause and unspecified) were not included in the main analyses. These classifications were based on ICD-10 categories and previous literature (Stillbirth Collaborative Research Network Writing Group, 2011). A detailed list of ICD-10 code and their descriptions are available in Table S1.

2.2. Pollution and source apportionment data

We investigated $PM_{2.5}$ total mass, $PM_{2.5}$ chemical constituents, and $PM_{2.5}$ sources. $PM_{2.5}$ total mass and chemical constituent levels from 2002/1/1 to 2009/12/31 were acquired from eight ambient monitors throughout California operated by the U.S. EPA, whose sampling frequency was every third or sixth day. Sampling sites were Bakersfield, El Cajon, Fresno, Los Angeles, Rubidoux, Sacramento, San Jose, and Simi Valley (Fig. S1). We considered the following 20 $PM_{2.5}$ constituents: aluminum (Al), ammonium ion (NH_4^+), calcium (Ca), choline (Cl), copper (Cu), elemental carbon (EC), iron (Fe), magnesium (Mg), nickel (Ni), nitrate ion (NO_3^-), organic carbon (OC), potassium (K), potassium ion (K^+), silicon (Si), sodium (Na), sodium ion (Na^+), sulfate ion ($SO_4^=$), titanium (Ti), vanadium (V), and zinc (Zn). These constituents were chosen based on our previous analyses and literature reviews (Ebisu and Bell, 2012; Basu et al., 2014; Ebisu et al., 2014).

Monitor-specific source apportionment modeling was performed using the Positive Matrix Factorization (PMF) receptor method to estimate $PM_{2.5}$ source levels for each observed date. Based on observed $PM_{2.5}$ constituents, the PMF receptor method estimates the amounts of $PM_{2.5}$ mass attributable to each source by constructing a chemical mass balance model (Reff et al., 2007). Five to nine sources were identified at each monitor. Following our previous studies (Ng et al., 2017; Ostro et al., 2016), we used five sources for the analyses: biomass burning, secondary ammonium nitrate, secondary ammonium sulfate, resuspended soil (i.e., road and soil dust), and vehicular emissions. It should be noted that $PM_{2.5}$ secondary ammonium sulfate and nitrate are not directly emitted, but instead formed through photochemical reactions of constituents that are mostly emitted by traffic and power plants (Hasheminassab et al., 2014a). Additional descriptions regarding monitor locations, sampling method, and PMF modeling are available elsewhere (Hasheminassab et al., 2014a, 2014b).

2.3. Exposure assessment

We assigned exposure levels of $PM_{2.5}$ total mass, five sources, and twenty constituents to mothers whose residential population-weighted ZCTA centroids were within 20 km of each monitor. To compare the same gestational periods between stillbirths and live births, we conducted a nested case-control study: matching one stillbirth (case) to five live births (controls) (see Section 2.4). First, full gestational exposure for mothers who experienced stillbirth were estimated. Weekly averaged pollutant levels were first calculated, and then combined to generate mean gestational exposure levels for mothers with stillbirth. After matching, we assigned gestational age-adjusted exposure levels to controls based on the gestational length of the matched case, regardless of the gestational lengths of the controls. For instance, if the gestational length of a stillbirth case was 33 weeks, the exposures for the controls were also calculated based on 33 weeks of exposure. By considering the same exposure time window, we made valid comparisons (Laurent et al., 2016b). Exposure level was not assigned for mothers whose weekly averaged levels were missing for more than 25% of the matched gestational length. This approach prevents bias from insufficient data (Ebisu and Bell, 2012).

We also estimated gestational age-adjusted exposure level of apparent temperature, which is calculated based on temperature and relative humidity (Kalkstein and Valimont, 1986). Temperature and relative humidity were obtained from the U.S. EPA, the California Irrigation Management Information System, and the National Oceanic Atmospheric Administration. The closest monitor to the maternal residential ZCTA was assigned, and the exposure levels were estimated following the same method described above.

2.4. Statistical analysis

To minimize confounding caused by individual factors and assign