Environmental Research 137 (2015) 268–277

Contents lists available at ScienceDirect

Environmental Research

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

Associations between prenatal traffic-related air pollution exposure and birth weight: Modification by sex and maternal pre-pregnancy body mass index

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ARTICLE INFO

Article history:
Received 22 August 2014
Received in revised form
29 October 2014
Accepted 31 October 2014

Keywords:
Traffic-related air pollution
Prenatal exposure
Birth weight
Sex
Body mass index

ABSTRACT

Background: Prenatal traffic-related air pollution exposure is linked to adverse birth outcomes. However, modifying effects of maternal body mass index (BMI) and infant sex remain virtually unexplored.
Objectives: We examined whether associations between prenatal air pollution and birth weight differed by sex and maternal BMI in 670 urban ethnically mixed mother–child pairs.
Methods: Black carbon (BC) levels were estimated using a validated spatio-temporal land-use regression (LUR) model; fine particulate matter ($PM_{2.5}$) was estimated using a hybrid LUR model incorporating satellite-derived Aerosol Optical Depth measures. Using stratified multivariable-adjusted regression analyses, we examined whether associations between prenatal air pollution and calculated birth weight for gestational age (BWGA) *z*-scores varied by sex and maternal pre-pregnancy BMI.
Results: Median birth weight was 3.3 ± 0.6 kg; 33% of mothers were obese (BMI ≥ 30 kg/m^3). In stratified analyses, the association between higher $PM_{2.5}$ and lower birth weight was significant in males of obese mothers (-0.42 unit of BWGA *z*-score change per IQR increase in $PM_{2.5}$, 95%CI: -0.79 to -0.06) ($PM_{2.5} \times$ sex $\times$ obesity $P_{interaction}=0.02$). Results were similar for BC models ($P_{interaction}=0.002$).
Conclusions: Associations of prenatal exposure to traffic-related air pollution and reduced birth weight were most evident in males born to obese mothers.

1. Introduction

Low birth weight remains a major public health problem. It is associated with increased infant mortality and developmental, behavioral, and metabolic disorders that may persist into adult life (Barker, 2003; Fisher et al., 2006; Johnson and Schoeni, 2011; McIntire et al., 1999). Thus, an active area of research examines modifiable environmental risk factors that impact birth outcomes (Nieuwenhuijsen et al., 2013). Increasing evidence suggests that outdoor ambient air pollution affects birth outcomes, including reduced birth weight (Dadvand et al., 2013; Nieuwenhuijsen et al., 2013; Shah and Balkhair, 2011; Stieb et al., 2012). Traffic-related air

Abbreviations: ACCESS, Asthma Coalition on Community, Environment, and Social Stress Project; BC, black carbon; BMI, body mass index; BWGA, birth weight for gestational age; PM2.5, particulate matter with a diameter of ≤ 2.5 μm; PM10, particulate matter with a diameter of ≤ 10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; PAH, polycyclic aromatic hydrocarbon; SES, socioeconomic status

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http://dx.doi.org/10.1016/j.envres.2014.10.035
0013-9351/

pollution, which remains a global public health problem especially in the urban environment, has been particularly implicated (Cohen et al., 2005; O'Neill et al., 2003; Proietti et al., 2013).

Studies have linked ambient and traffic-related air pollution to increased pro-inflammatory responses (Kannan et al., 2006; Ritz and Wilhelm, 2008) and systemic oxidative stress (Donaldson et al., 2001). While mechanisms linking ambient pollution to birth weight are not completely elucidated, overlapping evidence suggests that air pollution exposure may impact placental growth and function which in turn influences fetal growth. For example, animal studies have linked air pollution exposure with disrupted placental functional morphology in mice (e.g., reduced volume, caliber and surface area of maternal blood spaces, greater fetal capillary surfaces and diffusive conductance) (Veras et al., 2008). Moreover, various factors including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which play a role in placental vascular development as well as enzymes such as soluble fms-like tyrosine kinase-1 (sFlt-1) which may inhibit activity of these growth factors (Herraiz et al., 2014; Hoeben et al., 2004), may be influenced by air pollution exposures. For example, a recent human study links maternal exposure to particulate matter with a diameter $\leq 10\,\mu m$ (PM_{10}) and nitrogen dioxide (NO_2) with higher fetal sFlt-1 and lower PlGF levels (van den Hooven et al., 2012). It has been proposed that prenatal air pollution exposure likely involves enhanced maternal oxidative stress and inflammation causing decreased placental blood flow, disrupted trans-placental oxygenation and placental inflammation leading to impaired nutrient accretion for the fetus and in turn, decreased fetal growth (Donaldson et al., 2001; Kannan et al., 2006; Proietti et al., 2013; Yorifuji et al., 2012). Recently, prenatal PM_{10} exposure was found to be associated with mitochondrial alterations which can also intensify oxidative stress (Janssen et al., 2012). Other mechanisms of action have been proposed including endocrine disruption of hormones that regulate placental function and growth (Linton et al., 1993; Slama et al., 2008).

Multiple studies have examined associations between air pollution and adverse birth outcomes using different study designs, data collection methods and analytical approaches, each with their own strengths and limitations. Studies with larger sample sizes consider more chronic exposure to ambient air pollution and are usually based on birth certificates/registries without extensive information on individual factors, and have relied upon exposure assessments based on relatively crude estimates of ambient pollutants (e.g., proximity to roadways, exposure level measured by the closest monitoring site) and lack individual level information on personal and lifestyle characteristics or health behaviors which may confound the associations being examined (Ritz and Wilhelm, 2008). Exposure misclassification that results from the use of cruder proxies such as proximity to roadway, while likely non-differential, requires considerably large sample sizes to overcome. While studies using personal sampling may address some of these issues and hence yield better statistical power to detect associations (Dailey, 2009; Ponce et al., 2005), this approach is labor intensive and prohibitively costly for larger-scaled studies, typically includes exposure measurements at limited time points during pregnancy, and provides limited data on the geospatial distribution of pollution. Other researchers have used advanced spatio-temporal air pollution land-use regression (LUR) techniques to obtain estimates on exposure profiles throughout the pregnancy (Ghosh et al., 2012; Pedersen et al., 2013; Wilhelm et al., 2012). Recently, studies using prenatal particulate matter with a diameter of $\leq 2.5\,\mu m$ ($PM_{2.5}$) exposures estimated by a state-of-the-art modeling method that incorporates satellite-based data within a LUR framework also demonstrated significant associations with low birth weight and preterm birth (Hyder et al., 2014; Kloog et al., 2012). This approach yields daily estimates that can be aggregated to assess more chronic exposures to air pollution over the course of pregnancy.

In addition, few studies have focused on ethnic minorities and lower socioeconomic status (SES) urban populations, who are more likely to experience adverse birth outcomes (Dailey, 2009; Ponce et al., 2005; Wallace, 2011; Woodruff et al., 2003; Zeka et al., 2008) and may also be more likely to live in disadvantaged communities with increased exposure to traffic-related air pollution (O'Neill et al., 2003). In addition, evidence suggests that SES, including individual and neighborhood SES, and race might be associated with maternal obesity (Genereux et al., 2008). Studies to date have also not fully considered factors that may modify pollution effects on birth weight such as maternal pre-pregnancy obesity and infant sex (Bonzini et al., 2010; Ritz and Wilhelm, 2008).

Previous studies in non-pregnant adults suggest that obesity may modify the association between air pollution and adverse health outcomes (Baja et al., 2010; Dubowsky et al., 2006). Enhanced oxidative stress and inflammation are again implicated. For example, studies describe associations of higher ambient PM exposure with increased white blood cell count and systematic inflammatory markers, and demonstrate that obesity enhances these associations (Dubowsky et al., 2006). Moreover, pregnancy is a state having enhanced susceptibility to oxidative stress (Casanueva and Viteri, 2003; Patil et al., 2007) which has implications for fetal growth (Weber et al., 2014). These associations may be further modified by maternal obesity (Ferretti et al., 2014; Rajasingam et al., 2009; Sen et al., 2014).

Furthermore, evidence suggests that maternal height and weight may affect birth weight differentially in males and females (Lampl et al., 2010). Some studies demonstrate that male infants were at a higher risk of low birth weight in relationship to higher levels of air pollution compared with females (Ghosh et al., 2007; Jedrychowski et al., 2009), while others did not find statistically significant differences across sex (Bell et al., 2008; Pedersen et al., 2013). To our knowledge, only one study has examined effect modification by maternal obesity and found that maternal pre-pregnancy obesity significantly exacerbated the risk of polycyclic aromatic hydrocarbon (PAH) exposure on low birth weight in African-American newborns in a low income inner-city population (Choi and Perera, 2012). None have examined interactive effects of maternal obesity and sex concurrently.

Given these inter-connecting relationships we took advantage of an ethnically diverse urban sample of pregnant women to assess whether air pollution was associated with birth weight for gestational age and whether obesity and/or sex modified this relationship, while we were able to take into account a number of the potential confounders discussed above. Specifically, we examined the associations between prenatal maternal exposure to traffic-related ambient air pollutants [black carbon (BC), a surrogate of traffic particles, and ambient $PM_{2.5}$] and birth weight. The primary objective of these analyses was to examine interactions among prenatal air pollution, sex, and maternal obesity given overlapping evidence suggesting differential associations between ambient air pollution and birth outcomes related to maternal obesity and infant sex, as well as associations between maternal height and weight and infant growth that differ based on child sex.

2. Material and methods

2.1. Study participants

Between August 2002 to September 2009, English- or Spanish-speaking women ≥ 18 years old receiving prenatal care at the Brigham and Women's Hospital (BWH) and Boston Medical Center