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Prenatal exposure to $PM_{2.5}$ and birth weight: A pooled analysis from three North American longitudinal pregnancy cohort studies

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A B S T R A C T

A common practice when analyzing multi-site epidemiological data is to include a term for 'site' to account for unmeasured effects at each location. This practice should be carefully considered when site can have complex relationships with important demographic and exposure variables. We leverage data from three longitudinal North American pregnancy cohorts to demonstrate a novel method to assess study heterogeneity and potential combinability of studies for pooled analyses in order to better understand how to consider site in analyses. Results from linear regression and fixed effects meta-regression models run both prior to and following the proposed combinability analyses were compared. In order to exemplify this approach, we examined associations between prenatal exposure to particulate matter and birth weight. Analyses included mother-child dyads (N = 1966) from the *Asthma Coalition on Community Environment and Social Stress (ACCESS)* Project and the *PRogramming of Intergenerational Stress Mechanisms (PRISM)* study in the northeastern United States, and the *Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS)* study in Mexico City. Mothers' daily third trimester exposure to particulate matter ≤ 2.5 μm in diameter ($PM_{2.5}$) was estimated using a validated satellite-based spatio-temporally resolved model in all studies. Fenton birth weight for gestational age z-scores were calculated. Linear regression analyses within each cohort separately did not find significant associations between $PM_{2.5}$ averaged over the third trimester and Fenton z-scores. The initial meta-regression model also did not find significant associations between prenatal $PM_{2.5}$ and birthweight. Next, propensity scores and log linear models were used to assess higher order interactions and determine if sites were comparable with regard to sociodemographics and other covariates; these analyses demonstrated that PROGRESS and ACCESS were combinable. Adjusted linear regression models including a 2-level site variable according to the pooling indicated by the log linear models (ACCESS and PROGRESS as one level and PRISM as another) revealed that a 5 μg/m^3 increase in $PM_{2.5}$ was associated with a 0.075 decrease in Fenton z-score ($p < 0.0001$); linear models

Abbreviations: CI, confidence interval; LBW, low birth weight; $PM_{2.5}$, Particulate matter less than or equal 2.5 μm in diameter; PM_{10}, Particulate matter less than or equal 10 μm in diameter

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including a 3-level site variable did not reveal significant associations. By assessing the combinability of heterogeneous populations prior to combining data using a method that more optimally accounts for underlying cohort differences, we were able to identify significant associations between prenatal $PM_{2.5}$ exposure and birthweight that were not detected using standard methods.

1. Introduction

Ambient air pollution ranks among the top ten risk factors for global burden of disease (Lim et al., 2012). The fetus may be particularly susceptible to ambient air pollution exposure effects due to rapid development and immature detoxifying enzyme systems (Wells et al., 2009). Emerging evidence has linked prenatal exposure to both gaseous and particulate air pollution to a number of adverse fetal outcomes, including reduced growth and term low birth weight (LBW), typically defined as birthweight < 2500 g for newborns born at ≥ 37 completed weeks of gestation) (Fleisch et al., 2015; Lakshmanan et al., 2015; Morello-Frosch et al., 2010); however, an association between ambient pollution and lower birth weight has not been consistently demonstrated across studies. In a study in Japan that examined national health survey data, higher suspended particulate matter (SPM) and sulfur dioxide (SO_2) during pregnancy were associated with higher odds of term LBW (Yorifuji et al., 2015). A study of full term births in Massachusetts examined birth weight as a continuous outcome and reported that a 10 μg/m^3 increase in particulate matter less than or equal 2.5 μm in diameter ($PM_{2.5}$) levels during pregnancy was associated with a 13.80 g decrease in birth weight (Kloog et al., 2012). An analysis of birth records data in Canada found associations between $PM_{2.5}$ exposure during pregnancy and greater odds of small for gestational age (SGA) and greater reductions in term birth weight, but not LBW (Stieb et al., 2016). In a pooled analysis of 14 European birth cohorts across 12 countries, a 5 μg/m^3 average increase in $PM_{2.5}$ during pregnancy, estimated using land use regression (LUR), was associated with higher odds of term LBW (Pedersen et al., 2013). Notably, previous reports on individual cohorts included in the pooled analysis in Pedersen et al. (2013) did not find statistically significant associations between $PM_{2.5}$ and term birth weight (Gehring et al., 2011). In a meta-analysis of published literature on prenatal exposure to $PM_{2.5}$ and PM_{10} and adverse birth outcomes, Sapkota et al. reported increased odds of LBW with higher $PM_{2.5}$ exposure, but the results were not statistically significant and deemed inconclusive (Sapkota et al., 2012). In a study of singleton live births in California limited to full-term infants, only prenatal exposure to ozone, not $PM_{2.5}$ or NO_2, was associated with higher odds of term LBW (Laurent et al., 2016). In another study that examined spatial variation in the association between ambient air pollutants and birth weight of full-term singletons in the state of Georgia, ozone was positively associated with higher birth weight, whereas $PM_{2.5}$ was not associated with birth weight (Tu et al., 2016).

Discrepancies in these findings and methodological differences in studies (Dadvand et al., 2013; Woodruff et al., 2009) have limited the ability to synthesize the evidence and translate it into policy. These discrepancies may be attributable to differences in exposure assignment (e.g., land use regression (LUR) vs. dispersion models vs. monitor assignment), sample size, patterns of exposure dependent on geographic location, or the range of exposure and/or outcome within each population which limits the ability to find significant associations within a given study.

Increasingly, epidemiologic studies are combining data among multiple cohorts not originally designed as a consortium, such as the newly launched NIH Environmental influences on Child Health Outcomes (ECHO) program. Methods that can rigorously pool data in these scenarios are clearly needed. The integration of data from multiple pediatric environmental health studies has the potential to provide enhanced power and exposure contrast to examine associations between ambient air pollution and fetal outcomes. A common practice when analyzing multi-site epidemiological data is to include a term for 'site' to account for unmeasured effects at each location. However, this practice should be carefully considered when site can have complex relationships with important demographic variables and other covariates. For example, in order to properly integrate data, social factors that might influence exposure, such as racial/ethnic makeup and socioeconomic compositions of the cohorts of interest, should be taken into account more formally. Traditional meta-analysis do not deal with differences across cohorts, rather they compare effect estimates across studies. Covariates might be adjusted for within each study but differences in covariates are not adjusted for across studies. Developing tools that enhance our ability to combine multi-site data while accounting for study heterogeneity could be a significant methodological advancement.

The current study leveraged existing data from three established North American population-based birth cohorts, two in the northeastern United States (U.S.) and one in Mexico, to examine their potential combinability and to test associations between prenatal $PM_{2.5}$ exposure and infant birthweight in the integrated sample. We utilize estimates of air pollution during the third trimester of pregnancy in these analyses to illustrate a novel approach to assessing combinability of cohort data accounting for potential sociodemographic confounders and covariates.

2. Methods

2.1. Study cohorts

We included three prenatally enrolled cohorts based in the U.S. or Mexico with similarly derived air pollution measures. Here we provide details on enrollment procedures.

2.1.1. Asthma Coalition on Community Environment and Social Stress (ACCESS) project

Project ACCESS is a prospective cohort of mother-child dyads designed to study the effects of early life stress and other environmental factors on urban childhood asthma risk (Wright et al., 2008). Briefly, $N = 660$ English- or Spanish-speaking pregnant women (≥ 18 years of age) with singleton pregnancies receiving care at Brigham & Women's Hospital (BWH), Boston Medical Center (BMC), and affiliated community health centers were enrolled between August 2002 and January 2007. Data on sociodemographics, maternal health, and prenatal exposures included in these analyses were obtained within 2 weeks of enrollment. Procedures were approved by human studies committees at the Brigham and Women's Hospital and Boston Medical Center; written informed consent in the mother's primary language was obtained from all mothers.

2.1.2. PRogramming of Intergenerational Stress Mechanisms (PRISM) study

The PRISM study is a prospective pregnancy cohort of mother-child dyads originally designed to study how perinatal stress influences children's stress response systems over early development and subsequent respiratory health while controlling for environmental exposures (e.g., ambient air pollution, nutrition) (Brunst et al., 2014). Between March 2011 and August 2012, $N = 365$ women were recruited from prenatal clinics at the Beth Israel Deaconess Medical Center (BIDMC) and the East Boston Neighborhood Health Center in Boston, Massachusetts, U.S.A. English- or Spanish-speaking women with

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