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

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Abstract

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

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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 microns 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 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.

Keywords

air pollution; birth weight; propensity scores

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

microns 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 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). 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 and exposure variables. 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 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.

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.

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 singleton pregnancies were eligible if they were age 18 years at enrollment and endorsed drinking <7 alcoholic drinks/week prior to pregnancy and none since pregnancy recognition. Procedures were approved by human studies committees at the Brigham & Women's Hospital, Icahn School of Medicine at Mount Sinai (ISMMS), and BIDMC; written consent was obtained in the subject's primary language.

Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study—PROGRESS is a prospective birth cohort originally designed to study the modifying effects of stress on lead toxicity and on the neurotoxicity of metal mixtures. Pregnant women receiving prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social –IMSS) between July 2007 and February

2011 were recruited into the PROGRESS study (Burris *et al.*, 2013). Women were eligible to participate if they were less than 20 weeks pregnant, at least 18 years old, planned to stay in Mexico City for the next 3 years, had access to a telephone, had no medical history of heart or kidney disease, did not consume alcohol daily, and did not use any steroid or anti-epilepsy medications. Procedures were approved by institutional review boards at the Harvard School of Public Health, the Mexican National Institute of Public Health, and the ISMMS. Mothers provided written informed consent.

2.2 Ambient air pollution exposure estimates

Individuals' prenatal exposure to $PM_{2.5}$, an index of ambient pollution from traffic and other sources, was estimated based on residence during pregnancy (i.e., at enrollment and updated if they moved) using a validated hybrid satellite based spatio-temporal prediction model for all cohorts. For ACCESS and PRISM, the model incorporated Moderate Resolution Imaging Spectroradiometer (MODIS) derived aerosol optical depth (AOD) measurements at a 1×1 km spatial resolution, using day-specific AOD data calibrated against ground monitor-based $PM_{2.5}$ measurements derived from 78 monitoring stations covering New England (Kloog *et al.* 2014; Kloog *et al.* 2011; Nwanaji-Enwerem *et al.* 2016). The model incorporated traditional land use regression (LUR) and meteorological variables. For locations on days without AOD data (due to cloud coverage, snow, etc.), predictions were based on a regression of predicted $PM_{2.5}$ in that 1km cell on days when AOD was present against the mean of $PM_{2.5}$ monitors within 60 km of the cell, and a thin plate spline of latitude and longitude and a random intercept for each cell to impute predictions at these missing locations. The out of sample ten-fold cross validation R^2 for daily values was 0.88.

For PROGRESS, daily $PM_{2.5}$ levels across Mexico City were estimated at a 1×1 km spatial resolution at the participant's reported residence during pregnancy (Just *et al.* 2015). Similar to the model used for ACCESS and PRISM, the model was run using day-specific calibrations of AOD data calibrated against ground $PM_{2.5}$ measurements from 12 monitoring stations covering Mexico City and LUR and meteorological variables (roadway density, temperature, relative humidity, planetary boundary layer, and daily precipitation). As in previous studies, mixed effect models with spatial and temporal predictors and day-specific random effects were used to account for temporal variations in the $PM_{2.5}$–AOD relationship. For days without AOD data, the model was fit with a seasonal smooth function of latitude and longitude and time-varying average incorporating local monitoring. The out of sample ten-fold cross validation R^2 of 0.724. We use $PM_{2.5}$ exposure averaged over the third trimester of pregnancy to demonstrate our approach to assess combinability, to help reduce variability and increase precision of the estimates.

2.3 Birth weight z-score outcome

In ACCESS and PRISM, gestational age was calculated based on maternal report of last menstrual period (LMP) and updated based on obstetrical estimates based on ultrasound data from medical record review at delivery if discrepant by more than 3 weeks (Hoffman *et al.* 2008). IN PROGRESS, ultrasounds were not routinely performed as standard of care; thus, gestational age was based on LMP and by a standardized physical examination at birth to determine gestational age (Capurro *et al.* 1978). If the physical examination assessment of

gestational age differed by more than 3 weeks from the gestational age based on LMP, the estimate of gestational age based on physical exam was used. The Capurro and ultrasound methods have been found to have good concordance (Pereira *et al.*, 2013). Birth weight data were extracted from labor and delivery records for all studies. Given that birth weight is tightly tied to length of gestation, that each may have different predictors, and that birth weight rises in a non-linear pattern with increasing gestational age (Oken *et al.* 2003), traditional approaches that use raw birth weight data adjusted for gestational age in a linear regression model may add bias (Oken *et al.* 2003). Use of z-scores allows adjustment for gestational age more precisely, as z-scores factor in non-linear growth, which reduces both bias and residual confounding (Oken *et al.* 2003). Therefore, we derived Fenton birth weight for gestational age z-scores for all cohorts (Fenton *et al.* 2013). These reference curves were derived from a growth curve modeling meta-analysis of preterm birth and validated with the World Health Organization (WHO) growth curves for postnatal growth. Z-scores facilitate harmonization across different cohorts, including those from different countries (Fenton *et al.* 2013).

2.4 Covariates

Previously identified covariates related to air pollution exposure and birth weight were considered For all cohorts, maternal age, race/ethnicity, and maternal education as an indicator of individual-level socioeconomic status (SES) were ascertained by questionnaire Maternal pre-pregnancy height and weight were determined via self-report at enrollment; body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2). Sensitivity analyses were also carried out with the inclusion of report smoking during pregnancy ascertained through questionnaire.

2.5 Statistical Analysis

The overarching goal of the analysis was to compare results to fixed effects meta-regression and linear regression with adjustment for site to the proposed combinability approach. Thus we approached the analyses in the following stepwise manner. First in the standard approach, linear models were used to evaluate the association between third trimester $PM_{2.5}$ levels and birth weight for gestational age z-scores in each study separately. Models were adjusted for maternal education, race, age, and pre-pregnancy BMI. To address the possibility of unmeasured differences among the sites, a fixed effects meta-regression analysis was employed by extracting the beta coefficients and standard errors from the linear model stratified by the site variable. Next we examined the combinability of the ACCESS, PRISM, and PROGRESS data in two ways. First, propensity scores were estimated from multinomial logistic models with site as the outcome and education (high school or > higher school), race/ethnicity (white, non-Hispanic or non-white and/or Hispanic), BMI (maternal pre-pregnancy, continuous), gestational age (continuous), mother's age at birth (continuous), infant sex, and average third trimester $PM_{2.5}$ (continuous) as the predictors, while allowing for two- and three-way interactions among the predictor variables. Significant terms indicate complex characteristics of the studies that distinguish them from one another. Propensity scores are calculated by taking the inverse of the probabilities obtained from the multinomial logistic models and defined as the conditional probability of an individual belonging to their actual study given covariates. If the probability of being

assigned to any of the three studies is similar, it suggests that the sites are comparable in regard to the covariates. The distribution of the probabilities of an individual being assigned to each site was evaluated with boxplots.

Second, log-linear models of multidimensional contingency tables were used to detect and characterize heterogeneous inter-study association patterns (Agresti *et al.* 2002). Inter-study association patterns refer to interactions between the covariates, exposure and outcome particularly to determine if these were modified by study site. Deviance was used as a measure of fit. A significant deviance indicates that the nested model does not fit as well as the larger model. The variables considered were maternal education (high school or > higher school), site (ACCESS, PRISM, or PROGRESS) age (dichotomized at median), pre-pregnancy BMI (dichotomized at median), and for the purposes of the log linear models only, $PM_{2.5}$ was included in quartiles, and the outcome birth weight for gestational age z-score was dichotomized at the median. Log-linear models were such that 6-way, 5-way, 4-way, and 3-way site interaction terms could be systematically evaluated. Factors that were not adequately diverse (i.e., PROGRESS included only Hispanics, PROGRESS being predominantly non-smoking) were not included in log-linear models. Log linear models were used in order to determine grouping; exclusion of variables in this step did not preclude their inclusion in the models after grouping was decided. Model construction followed with the model fully parameterized with terms not including site and where k-way site interaction terms were tested for significance in a top-down strategy (i.e., 6-way interaction, then all 5-way interaction terms, etc.) Alpha was set at 10%. All significant *site* interactions were further explored with odds ratios (OR).

Finally, linear models were used to evaluate the association between third trimester $PM_{2.5}$ and birth weight for gestational age z-scores, both as continuous variables, according to the pooling indicated by the log linear models. Models were adjusted for maternal education, race, age, and pre-pregnancy BMI.

3. Results

3.1. Descriptive statistics

As seen in Table 1, many of the demographic characteristics varied across the ACCESS, PRISM, and PROGRESS cohorts. Notably, PROGRESS, which was recruited in Mexico, included 100% Hispanic participants whereas 90% of ACCESS and 64% of PRISM participants were non-white and/or Hispanic. In ACCESS and PROGRESS, mothers had similar education levels (61% and 76% high school, respectively), whereas the majority of women in PRISM had >high school education (73%). PROGRESS had lower mean birth weight z-scores, whereas ACCESS and PRISM birth weight z-scores were more similar. The distribution of infant sex was consistent across studies. PROGRESS had the highest levels of $PM_{2.5}$ (mean: 23.1 μg/m^3) while PRISM had the lowest levels of $PM_{2.5}$ (mean: 8.23 μg/m^3).

3.2. Linear regression and meta-regression models prior to combinability analysis

We first show results from the linear regression and fixed effect meta-regression analysis. Table 2 shows the linear model associations for each individual study and the estimated

results of a meta-regression combining the betas and standard errors from the adjusted linear regression models. (i.e., all 3 study sites considered individually). The associations between third trimester $PM_{2.5}$ and birth weight z-score are negative in PRISM and PROGRESS and in the overall meta-regression but these results did not reach statistical significance in the individual cohorts. A limitation of the meta-regression model is that it does not benefit from differences in the exposure range across studies; that is, the slope estimates are combined without regard to the variable range of the exposure within each study. Specifically, PROGRESS has higher $PM_{2.5}$ values with non-overlapping IQRs with ACCESS and PRISM (Table 1) yet this expanded exposure range across studies is not taken advantage of in the meta-regression.

3.3. Combinability analyses

We next examined the combinability of the three studies. Figure 1 shows that the distribution of the probability of being assigned to the three studies varied; thus, differences in covariate and exposure distributions predict study identification. In particular, significant model terms indicated the existence of higher-level interactions. We also explored these interactions excluding $PM_{2.5}$ and found PRISM was more distinct compared to the similarities in ACCESS and PROGRESS. For additional insight, we continued with further analysis of combinability through log-linear models.

In the next step, log-linear models were used to systematically evaluate 6-way, 5-way, 4-way, and 3-way site interaction terms (Table 3). Deviance was used as a measure of fit and a significant deviance indicates that the nested model does not fit as well as the larger model. Log-linear models detected a 3-way site interaction, which indicated heterogeneous inter-study association patterns (Table 4). We did not see a significant interaction between $PM_{2.5}$, birthweight and study which would indicate that the association of interest is similar across studies. We identified that the association between maternal age and BMI differed among the sites (p=0.001). Figure 2 shows a further examination of this association using odds ratios to compare the odds of younger mothers (maternal age <median) having low BMI (<median) when compared to the odds of younger mothers having high BMI (>median). The OR for PRISM was statistically different from ACCESS and PROGRESS which saw associations in the same direction and of similar magnitude. We also found that the association between maternal BMI and birth weight for gestational age z-score differed among sites. Similar to Figure 2, Figure 3, compares the odds of mothers with low BMI having a baby with birth weight z-score below the median when compared to the of mothers with low BMI having a baby with a birth weight z-score above the median. The OR for this association in PRISM differed in directionality from the ORs seen in PROGRESS and ACCESS (Figure 3). In conclusion, the propensity scores implied differences across sites due to high level interactions. Similarly, the log-linear models and ORs suggested that the association patterns among covariates were similar for ACCESS and PROGRESS. Therefore, we combined the ACCESS and the PROGRESS data as a single "surrogate study".

3.4. Linear regression and meta-regression models informed by combinability analyses

Table 5 shows adjusted linear regression models with a 2-level site variable (ACCESS and PROGRESS as one level and PRISM as another) and a 3-level site variable. The 2-level site model found a significant association (p<0.0001) between third trimester $PM_{2.5}$ and birth weight for gestational age z-scores; a 5 μg/m^3 increase in third trimester $PM_{2.5}$ levels was associated with a 0.075 decrease in birth weight for gestational age z-score. The linear regression model including a 3-level site variable did not find a significant association (p=0.92) between $PM_{2.5}$ and birth weight z-score – the primary association of interest.

The fixed effects meta-regression informed by the combinability analysis, which summarized the results from one model with ACCESS and PROGRESS and a second model with PRISM, also identified a negative association between third trimester $PM_{2.5}$ levels and birth weight for gestational age z-scores (Table 6) of similar magnitude to the first model.

Figure 4 shows an overall negative association between third trimester $PM_{2.5}$ and the adjusted birth weight for gestational age z-score. The slope for PRISM differed from the slope for ACCESS and PROGRESS, which may suggest a non-linear association between birth weight for gestational age z-score and $PM_{2.5}$. Results that included report of smoking paralleled those reported here (see Supplemental material).

4. Discussion

These analyses leveraged data from three North American pregnancy cohorts to exemplify a novel method to assess study heterogeneity and potential combinability of studies for pooled analyses to better inform how to consider site in these analyses. We exemplify these methods in analyses examining associations between ambient $PM_{2.5}$ exposure and infant birth weight. Notably, these studies took the same approach to modeling air pollution exposures and characterized the outcome using birth weight adjusted for gestational age Fenton z-scores given that both U.S. and international participants were included and z-scores allowed us to include all children and not limit our analysis to only full term children as has been done in previous studies. The combinability approach reported here used propensity scores and log linear models to evaluate higher dimensional associations that serve to indicate heterogeneous inter-study association patterns. The patterns that emerged indicated that these underlying associations were similar between the ACCESS and PROGRESS studies and that these two studies were combinable. Prior to assessing combinability, we did not find a significant association between prenatal $PM_{2.5}$ and birthweight in analyses considering each cohort separately or the meta-regression which combined the linear regression estimates from the 3 cohorts. Linear models combining studies according to the pooling indicated by the log linear models revealed a significant association between increased levels of third trimester $PM_{2.5}$ and lower birth weight for gestational age in analyses combining ACCESS and PROGRESS cohort data. The observed associations remained significant after adjustment for potential sociodemographic confounders and other covariates including maternal smoking.

The combinability method presented here allows for the adjustment of known variables across cohorts and minimizes the potential impact of the unknown confounders that "site"

might represent. Moreover, the combinability approach takes better advantage of the increased heterogeneity in exposure across studies compared to an analysis simply adjusting for a 3-level site indicator. Notably, significant associations were seen only after combining ACCESS (a cohort in the northeastern U.S.) and PROGRESS (Mexico City sample) likely in part to limited within study exposure contrasts. While the Mexico City sample had higher $PM_{2.5}$ exposure values with non-overlapping IQRs when compared to the northeastern U.S. samples, we are able to increase exposure contrast by combining it with the ACCESS cohort. This also expanded the range in values for the outcome. This coupled with increased sample size in the pooled analysis likely contributed to enhanced power to detect effects relative to analyses performed prior to assessing combinability.

It is worth pointing out that our results are in line with other global research showing associations between *in utero* $PM_{2.5}$ exposure later in pregnancy and birth weight. In Beijing, a 19.8 μg/m^3 increase in $PM_{2.5}$ during the 8th month of gestation was associated with an 18 g decrease in birth weight (Rich *et al.* 2015). In an analysis of data from the World Health Organization Global Survey on Maternal and Perinatal Health from 2004 through 2008, an increase in seasonally adjusted $PM_{2.5}$ levels estimated in the month preceding delivery were associated with higher odds of low birth weight in a pooled analysis of 22 countries (Fleischer *et al.* 2014). In a study of pregnancy outcomes in Canada, $PM_{2.5}$ exposure late in pregnancy was reported to have stronger associations with SGA and term birth weight than exposure in early and mid- pregnancy (Stieb *et al.* 2016). We reiterate that we utilized third trimester estimates of air pollution in these analyses to illustrate the approach to assessing combinability of cohort data. While some studies report significant associations between $PM_{2.5}$ exposure in later pregnancy, others show associations in the first trimester or do not identify specific vulnerable windows (Hao *et al.* 2016) (Dadvand *et al.* 2013). Such disparate findings related to the exposure timing in this field are likely related to various methodological issues across studies (Woodruff *et al.* 2009). Consideration of timing of exposure is another challenge to doing pooled analysis of observational studies in this field and was beyond the scope of our current demonstration.

As the main purpose of our presented analysis was to exemplify a novel combinability approach for pooled analyses, we acknowledge some limitations relative to the specific associations being examined. We did not consider air pollution exposures in microenvironments that might lead to personal exposure levels that differed from our ambient exposure estimated at the home residence. The covariates used to determine the combinability of the studies were not exhaustive and we cannot rule out the possibility that additional variables might yield different results. The analyses were limited to the covariates that were available for all three studies which had adequate diversity as noted previously. Mother's prenatal smoking status was not considered in the main analysis for a number of reasons. The distribution of $PM_{2.5}$ levels did not vary by report of maternal smoking in any of the 3 cohorts (Supplemental table S1). Inclusion of maternal smoking did not alter the distribution of propensity scores (Figure S1). Maternal smoking was excluded from the log linear model step used to determine grouping due to inadequate diversity (PROGRESS being practically non-smoking). Moreover, studies indicate that tobacco smoke exposure is a major contributor to indoor air pollution in inner-city homes (Wallace *et al.* 2003) (McCormack *et al.* 2009) and that variations in indoor source particles (e.g., from smoking and/or cooking

sources) are largely uncorrelated with variations in outdoor source particles, which is the main exposure considered herein (Wilson *et al.* 2000). Thus, while particles of indoor origin are an important predictor of fetal development in and of themselves, they are unlikely to confound associations between ambient particulate matter and birthweight. In secondary analyses presented in supplemental material, we show that inclusion of maternal smoking modestly strengthened the association between $PM_{2.5}$ and birth weight z-score after grouping PROGRESS and ACCESS together in both the analyses using the surrogate study variables (Table S3) and the meta-regression (Table S4). Nonetheless, we cannot rule out potential residual confounding due to unmeasured host and environmental factors that may influence birth weight.

Pooled analyses of longitudinal observational studies are increasingly being done to inform policy and public health. Meta-analysis of observational studies present particular challenges given heterogeneity in the distribution of covariates across studies and variable design. We demonstrate that assessing the combinability of heterogeneous populations prior to combining their data may allow for a better understanding of underlying cohort differences and provide increased power to detect associations that would be undetected by more customary methods for combining cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

CI   confidence interval

LBW   low birth weight

$PM_{2.5}$ Particulate matter less than or equal 2.5 microns in diameter

PM_{10}   Particulate matter less than or equal 10 microns in diameter

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Highlights

- Examined association between prenatal $PM_{2.5}$ and birth weight data from 3 studies.

- Used novel combinability method to integrate data, account for study heterogeneity.

- PROGRESS and ACCESS studies were comparable with regard to covariates.

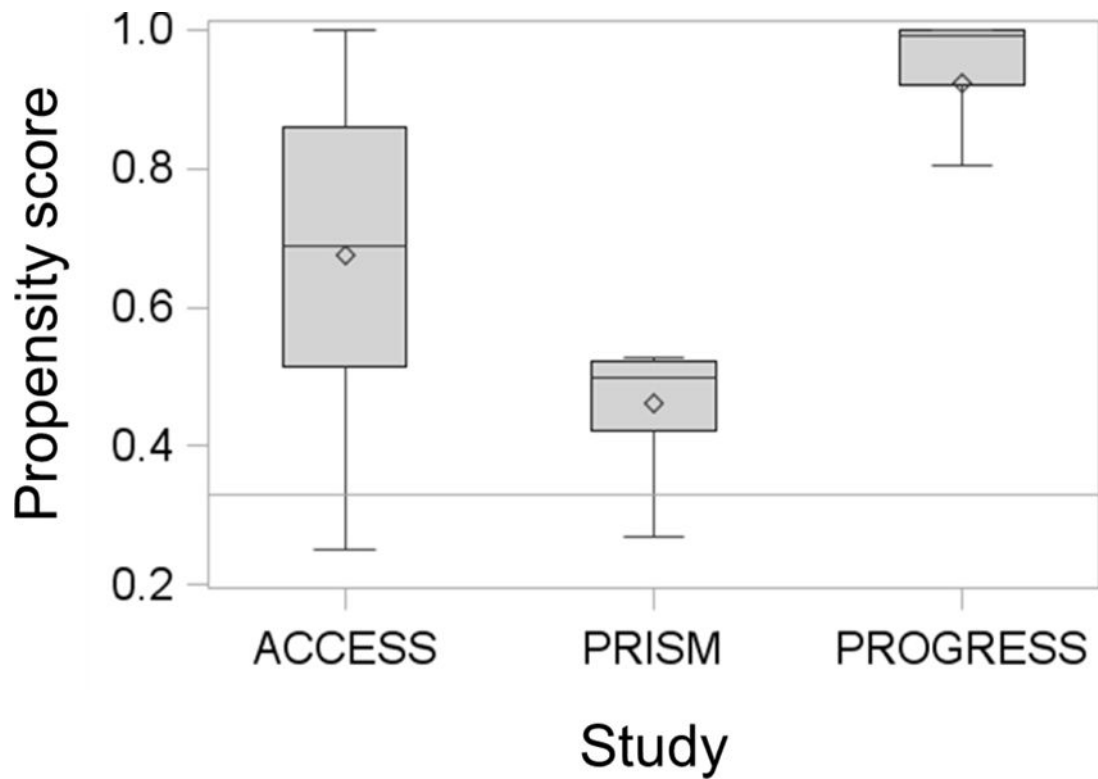- Higher 3rd trimester $PM_{2.5}$ associated with lower BWGA **z-scores**.

Figure 1.
Distributions of propensity scores by cohort study. Box plots depicting propensity scores for ACCESS, PRISM and PROGRESS. Propensity scores are defined as the conditional probability of an individual belonging to their actual study given covariates. Line in the box plot depicts the median, the diamond depicts the mean, the lower and upper bounds of the box depict the first and third quartile respectively, and the whiskers depict the minimum and maximum propensity score values for each cohort.
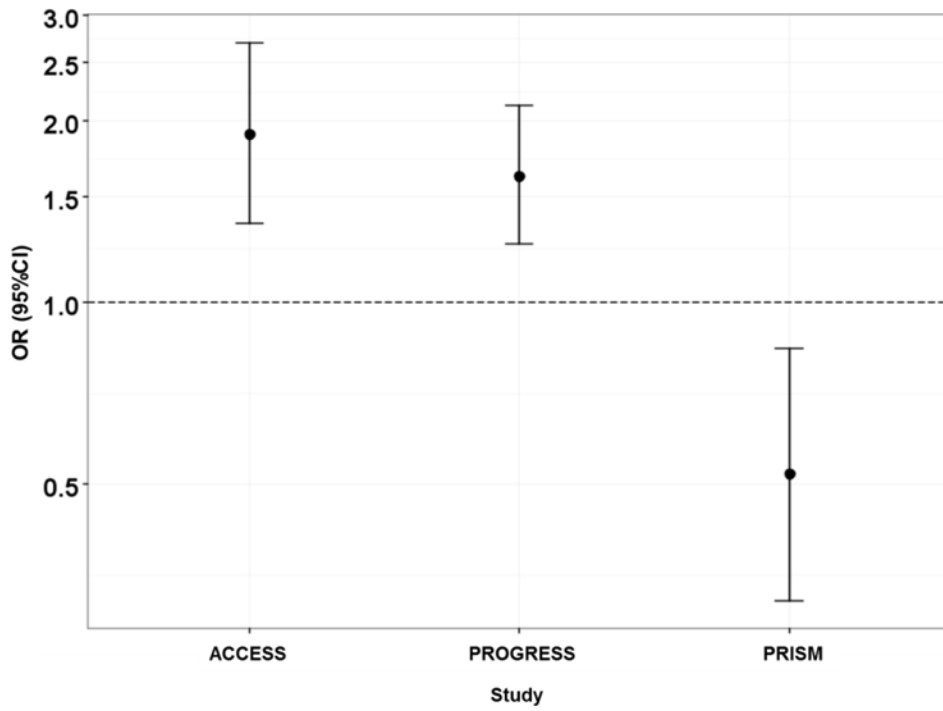
Figure 2.
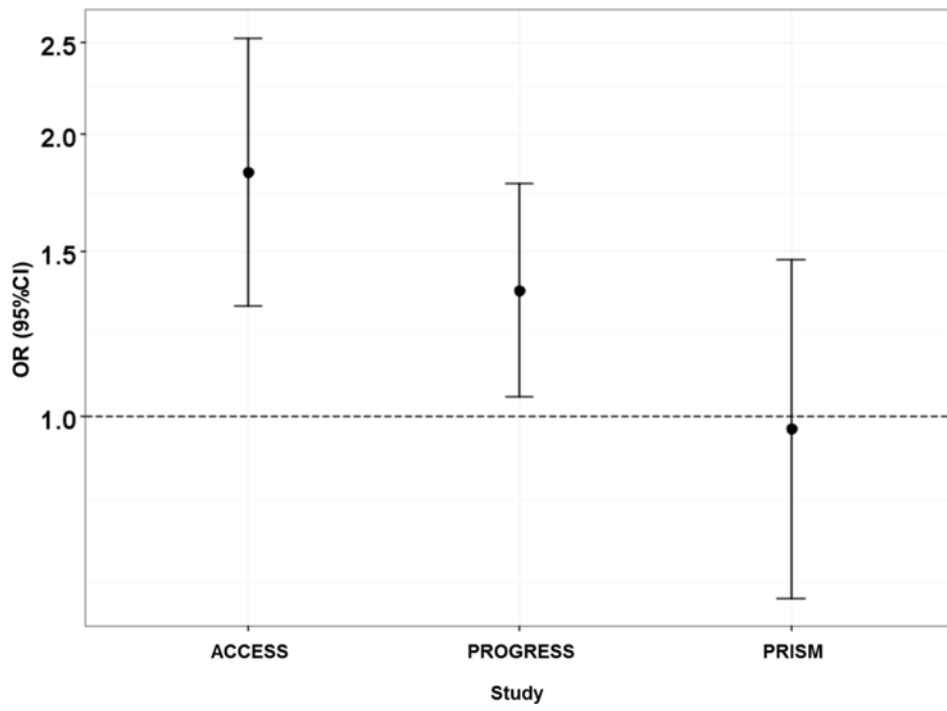Association between maternal pre-pregnancy BMI and maternal age by site.

Figure 3.
Association between maternal pre-pregnancy BMI and infant birth weight for gestational age Fenton z-score
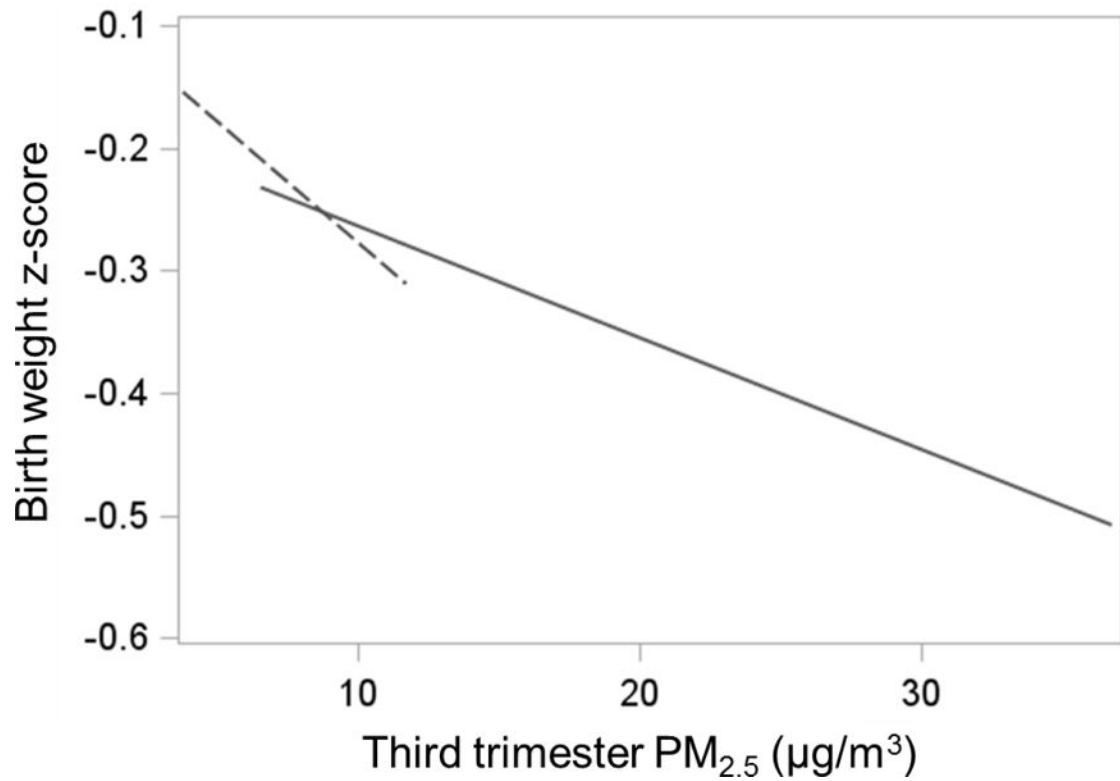
Figure 4. Site specific linear model within range of exposure: Cohort combinations based on log-linear models

Birth weight z-scores were constructed from the residuals of the pooled analysis linear model that regressed birth weight for gestational age z-scores by maternal education, race/ethnicity, age, and pre-pregnancy BMI and the overall mean birth weight for gestational age z-score was added to the residuals. Dotted line depicts estimate for the PRISM study. Solid line depicts estimate for ACCESS and PROGRESS combined.

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Table 1

Descriptive characteristics for pooled sample and individual cohorts

		Pooled Sample	ACCESS	PRISM	PROGRESS
N		1966	660	365	941
3rd trimester $PM_{2.5}$ ($\mu g/m^3$) [*]		16.27 (15.93, 16.61)	10.75 (10.62,10.88)	8.23 (8.09, 8.38)	23.13 (22.8, 23.46)
Birth weight for gestational age z-score [*]		−0.24(−0.29, −0.19)	−0.09 (−0.19,0.00)	−0.11 (−0.21, −0.02)	−0.46 (−0.52, −0.39)
Maternal pre-pregnancy BMI [*]		26.6 (26.34, 26.86)	28.8 (28.3, 29.3)	25.93 (25.3, 26.55)	25.23 (24.94, 25.52)
Maternal age at enrollment [*]		28.37 (28.12, 28.64)	27.1 (26.64, 27.56)	31.5 (30.94, 32.06)	28.04 (27.69, 28.39)
Sex [*]	Male	52%	52%	51%	52%
	Female	48%	48%	49%	48%
Race/Ethnicity [*]	White, Non-Hispanic	10%	10%	36%	0%
	Non-White and/or Hispanic	90%	90%	64%	100% [*]
Education [*]	High School	62%	61%	27%	76%
	> High School	38%	39%	73%	24% [*]

Means (95% CI) shown

[*] $P < 0.05$, differences tested using ANOVA for continuous variables and Chi-Square for dichotomous variables

Table 2

Linear regression models within each study and fixed effects meta-regression assessing the relationship between $PM_{2.5}$ and Fenton z-scores: Prior to combinability analyses

	N	Linear Models[†]		Meta Regression[‡]	
		β* (95% CI)	*P*-value	β (95% CI)	*P*-value
ACCESS	660	0.036 (−0.017, 0.089)	0.181	−0.0015 (−0.013, 0.009)	0.786
PRISM	365	−0.031 (−0.098, 0.036)	0.362		
PROGRESS	941	−0.002 (−0.014, 0.009)	0.670		

*
β represents the change in birth weight z-score per 1 unit increase in third trimester $PM_{2.5}$ ($\mu g/m^3$) levels

[†]Linear models were adjusted for maternal education (high school or > higher school), race/ethnicity (white/non-Hispanic or non–white and/or Hispanic), age at birth (continuous), and pre-pregnancy BMI (continuous).

[‡]Meta-regression showing results for the combination of the 3 separate study estimates obtained from adjusted linear regression models.

Table 3

Log-linear models

Model	Model Description	Notation	Deviance	DF
1	Saturated Model	(TEABPW)	0.00	0
2	Model excludes 6-way site interaction	(T(EABPW @ 5), EABPW)	0.12	1
3	Model excludes 6- and 5-way site interactions	(T(EABPW @ 4), EABPW)	4.16	7
4	Model excludes 6-, 5-, and 4-way site interactions	(T(EABPW @ 3), EABPW)	16.22	21
5	Model excludes 6-, 5-, 4-, and 3-way site interactions	(T(EABPW @ 2), EABPW)	45.17	41

Education (E); mother's age at birth (A); BMI (B); $PM_{2.5}$ (P); birth weight for gestation age Fenton z-score (W); site (T).

Table 4

Comparison of log-linear models

Model	Test Interactions	P-value	Sig Interactions (P <0.1)
1 vs 2	6-way site int	0.73	None
2 vs 3	5-way site int	0.67	None
3 vs 4	4-way site int	0.60	None
4 vs 5	3-way site int	0.09	TBA, TBW

Mother's age at birth (A); BMI (B); site (T); Fenton z-score (W)

Table 5

Linear models with and without surrogate study variable for the association between $PM_{2.5}$ over pregnancy and birth weight for gestational age z-score.

Model	β	95% CI	*P*-value
1[*]	−0.001	−0.013, 0.011	0.92
2[#]	−0.015	−0.022, −0.008	<0.0001

β represents the change in birth weight z-score per 1 unit increase in $PM_{2.5}$ (μg/m^3) during thethird trimester of pregnancy

Adjusted for maternal education (high school or > higher school), race/ethnicity (white/non-Hispanic or non-white and/or Hispanic), age at birth (continuous), and pre-pregnancy BMI (continuous).

[*] Model 1: Includes study variable (ACCESS, PROGRESS, PRISM)

[#] Model 2: Includes surrogate study variable, Surrogate Site 1 (PROGRESS and ACCESS) and Surrogate Site 2 (PRISM).

Table 6

Fixed effects meta-regression of linear model assessing the relationship between third trimester $PM_{2.5}$ and birth weight for gestational age z-score: Cohort combinations based on log-linear models

| | N | Linear Models[†] | | Meta Regression[‡] | |
		β* (95% CI)	P-value	β* (95% CI)	P-value
Surrogate Study 1 [#]	1601	−0.013 (−0.020, −0.005)	0.001	−0.0129 (−0.020, −0.006)	0.0001
Surrogate Study 2 [¶]	365	−0.031 (−0.098, 0.036)	0.362		

*
β represents the change in birth weight z-score per 1 unit increase in PM2.5 ($\mu g/m^3$) during the third trimester of pregnancy.

[#]
Surrogate Study 1 refers to ACCESS and PROGRESS.

[¶]
Surrogate Study 2 refers to PRISM.

[†]
Linear models adjusted for maternal education (≤ high school or > higher school), race/ethnicity (white/non-Hispanic or non-white and/or Hispanic), age at birth (continuous), and pre-pregnancy BMI (continuous).

[‡]
The meta-regression shows the results for the combination of the surrogate study estimates obtained from adjusted linear regression models.