The Impacts of Environmental Exposures on Birthweight

THE IMPACTS OF ENVIRONMENTAL EXPOSURES ON BIRTHWEIGHT

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Abstract

Environmental exposures have long been linked to health outcomes. This dissertation focuses on one outcome in particular, birthweight, as it is predictive of health status over the life course. The birth records of Massachusetts from 2001 to 2013 serve as the study population.

The first study considers particulate matter under 2.5 μm in aerodynamic diameter ($PM_{2.5}$), a well-established exposure risk for health detriments and decreased birthweight. Specifically, it seeks to quantify the associations between maternal exposure to $PM_{2.5}$ and birthweight at different points along the birthweight distribution. This study finds that the negative associations between fine particulate air pollution and birthweight were more severe among lighter newborns than heavier newborns, even after adjustment for potential sources of confounding. The second study narrows the focus onto chemical constituents of $PM_{2.5}$. It assesses the relative toxicities of elemental carbon, organic carbon, nitrate, and sulfate on birthweight while simultaneously adjusting for total fine particulate air pollution. It finds that elemental carbon was most toxic. The third study shifts away from $PM_{2.5}$ and explores surrounding greenness around the maternal residence as an exposure. It finds that increased maternal exposure to greenness was associated with birthweight and that this association is nonlinear. The fourth and final study applies a measure of neighborhood social stress and privilege as an exposure. Measures of racial and economic segregation are calculated and their associations with birthweight are assessed. It finds that higher values of these measures are positively associated with birthweight and that these relationships are modified by individual maternal race and Medicaid status.

The results from this dissertation inform air pollution control policy and urban planning, and identify those who are most vulnerable to environmental exposures. Analyses with novel exposures such as surrounding greenness and neighborhood social stress and privilege show that they are potentially important determinants of health and should be considered alongside well-established environmental exposures in future work.

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Introduction

Decreased birthweight is a risk factor for chronic diseases in later life (Belbasis et al. 2016; Hack et al. 1995). It has previously been shown that maternal exposure to environmental exposures such as air pollution are associated with decreased birthweight (Sun et al. 2016). In this dissertation, I estimate the effects of four maternal exposures during pregnancy, particulate air pollution under 2.5 μm in diameter ($PM_{2.5}$), individual constituents of $PM_{2.5}$, surrounding greenness, and neighborhood social stress and privilege on newborn birthweight.

$PM_{2.5}$ is a risk factor for chronic disease and mortality risk in adulthood (Cohen et al. 2017). Maternal exposure to $PM_{2.5}$ during pregnancy has been shown to be negatively associated with continuous birthweight (Basu et al. 2014; Ebisu and Bell 2012; Sun et al. 2016). Thus, $PM_{2.5}$ can be considered to be toxic to human health. For the first study in this dissertation, I ask if the negative association between $PM_{2.5}$ and birthweight is the same for newborns across the birthweight distribution. To do this, I use quantile regression, which is seldom applied in large epidemiologic studies. In the second study, I compare the relative toxicity of specific $PM_{2.5}$ constituents elemental carbon, organic carbon, nitrate, and sulfate. Research into how these major constituents are associated with birthweight is lacking and understanding which constituents are most toxic lead to more specific and impactful air pollution control policy.

The third and fourth studies involve emerging exposures in the field of environmental epidemiology. Surrounding greenness is thought to have health benefits by increasing access to recreation leading to higher physical activity and social contact, relieving mental stress and fatigue, and even buffering air pollution (Frumkin et al. 2017; James et al. 2015). Prior studies have suggested a positive association but have not explored the shape of this relationship. In the fourth and final study, I apply measures of neighborhood social stress and privilege and explore their associations with birthweight. These measures of neighborhood social stress and privilege are novel to the field of environmental epidemiology. In both of these two studies, I explore possible effect modification by indicators of individual socioeconomic status, which include maternal race, Medicaid support for prenatal care, and maternal education.

The source of the birthweight data is the Massachusetts Department of Public Health, which maintains a registry of birth records. In addition to birthweight, these birth records contain information on maternal characteristics, which can be sources of confounding in the relationship between environmental exposures and birthweight. These are considered as covariates in my analyses and are important in estimating effects from the environmental exposures considered in this dissertation.

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Study 1. Maternal Exposure to Fine Particulate Air Pollution during Pregnancy: Differences in Associations along the Birthweight Distribution

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Abstract

Background: Exposure to fine particulate air pollution ($PM_{2.5}$) during pregnancy is associated with detrimental birth outcomes, including lower birthweight. Existing estimates of the lower birthweight typically quantify the average change for entire study populations and do not inform on differential associations at different points of the birthweight distribution.

Objectives: In a large birth cohort, we used quantile regression to estimate changes to birthweight associated with $PM_{2.5}$ increases at each decile of birthweight and compare them to the average change.

Methods: We restricted our analyses to full-term live singleton births born in Massachusetts between 2001 and 2013 (n = 775,768). Using clinical gestational age and maternal residential address reported at the time of birth, average $PM_{2.5}$ exposure for the entire pregnancy was calculated. We estimated changes to birthweight per interquartile range (IQR) increase in $PM_{2.5}$ (2.3 $\mu g/m^3$). The final model included birth, maternal, and community covariates that describe the health and socioeconomic status (SES).

Results: An IQR increase in $PM_{2.5}$ was associated with a 16.07 (95% CI: 13.45, 18.69) g decrease in birthweight on average, 19.57 (95% CI: 15.67, 23.51) g decrease at the lowest decile of birthweight, and 13.80 (95% CI: 8.79, 18.67) decrease at the highest decile. The magnitudes of negative associations were larger in lower deciles. We did not find evidence for effect modification by individual and community level SES.

Conclusions: $PM_{2.5}$ and birthweight was negatively associated with disproportionately more severe associations at the lower quantiles of birthweight.

Introduction

Exposure to particulate air pollution under 2.5 µm ($PM_{2.5}$) is associated with increased mortality and morbidity, and is a leading cause of the global disease burden (Cohen et al. 2017). During the prenatal period, the fetus is susceptible to maternal environmental exposures such as $PM_{2.5}$ (Stillerman et al. 2008). In fact, increased prenatal exposure to $PM_{2.5}$ has previously been associated with decreased birthweights (Basu et al. 2014; Dadvand et al. 2013, 2013; Ebisu and Bell 2012; Kloog et al. 2012; Stieb et al. 2012; Sun et al. 2016). Lower birthweights are detrimental to the newborns' health as they are correlated with subsequent risk for chronic conditions such as including cardiovascular disease, diabetes, obesity, respiratory disease, and premature mortality (Belbasis et al. 2016; Boulet et al. 2011; Demerath et al. 2007; Hack et al. 1995; Korten et al. 2016; Reyes and Mañalich 2005). Prior studies have also shown that the associations between particulate air pollution and birthweight are modified by maternal socioeconomic status (SES) (Erickson et al. 2016; Ng et al. 2017; Westergaard et al. 2017). However, it remains uncertain how SES modifies the associations and if certain population subgroups are more susceptible to $PM_{2.5}$ than others.

In studying the relationship between $PM_{2.5}$ and birthweight, researchers have almost exclusively used generalized additive models and their simpler linear relatives to estimate the change in the mean birthweight associated with an increase in $PM_{2.5}$ (Stieb et al. 2012; Sun et al. 2016). While these models inform on the overall associations of $PM_{2.5}$ on the study population, they do not report on differences in associations across the birthweight distribution (Koenker 2005). In this study, we use quantile regression to study the relationship between $PM_{2.5}$ and birthweight, allowing us to estimate the associations of $PM_{2.5}$ with specific quantiles of birthweight. Quantile regression has previously been applied in studies of birthweights first with maternal behaviors and more recently with prenatal exposures to heavy metals, finding different associations in lower quantiles of birthweight compared to higher quantiles (Abrevaya 2001; Rahman et al. 2017; Rodosthenous et al. 2017). In contrast to more commonly-used regression techniques such as simple linear regression, quantile regression has the advantage that it makes no assumptions about the form of the distribution of outcome, but rather estimates the quantiles empirically (Koenker and Bassett 1978). With quantile regression, no assumption of normality of the birthweight distribution is required.

In addition to applying a seldom-used statistical method in particulate air pollution research, this study uses highly-resolved spatial and temporal $PM_{2.5}$ predictions to minimize exclusion due to missing exposure data. In some prior studies that rely on data from air pollution monitoring, those living far away from a monitoring station were excluded from analysis (Basu et al. 2014; Darrow et al. 2011; Ebisu and Bell 2012; Wilhelm et al. 2012). To fill in the missing gaps in air pollution monitoring, land use regression using variables such as traffic density has been used to estimate $PM_{2.5}$ concentrations, which can lead to biased estimates of the $PM_{2.5}$ effect in areas of low traffic density (Pedersen et al. 2013; Zeger et al. 2000). The generalizability of such models to less densely populated areas is also limited by the dearth of monitoring in such areas for model calibration, and the temporal resolution is often limited, generally to periods longer than a pregnancy. More sophisticated hybrid models, which use satellite remote sensing data in addition to land use and meteorological variables, have been developed to improve prediction accuracy and expand coverage (Kloog et al. 2014). Using satellite remote sensing data not only increases coverage of the study population, but also the temporal resolution. In this study, $PM_{2.5}$ exposure is based on a hybrid model that that predicts at a temporal resolution of 1 day and spatial resolution of 1 km * 1 km.

In summary, we investigate the association between $PM_{2.5}$ and birthweight at different points along the birthweight distribution using quantile regression and $PM_{2.5}$ exposure estimated at a high spatiotemporal resolution using geocoded maternal residential addresses.

Methods

Study Population

The study population included 978,225 births from the Massachusetts Birth Registry for the period between January 1, 2001 and December 31, 2013. At the time of birth, the residential address of the mother was recorded and later geocoded by the Massachusetts Department of Public Health against TomTom Multinet using AccuMail address and zipcode as the input address field and zone. 23,947 births were missing address information and 10,345 births living further than 2 km from a $PM_{2.5}$ prediction cell centroid were excluded. In our analysis, we restricted the data set to singleton, full-term live births with a minimum birthweight of 500 grams and a clinical gestational age between 37 and 44 weeks, which excluded 127,076 births. Further restriction to those with complete data on the regression covariates excluded 41,093 births, with the majority missing data on parity, leading to a final sample size of 775,768. This use of birth data was approved by the Massachusetts Department of Public Health as well as the human subjects committee at the Harvard T. H. Chan School of Public Health.

$PM_{2.5}$ Exposure

For each birth, the clinical gestational age and maternal geocoded address were used to calculate the average prenatal $PM_{2.5}$ exposure. Specifically, each birth was assigned to the closest 1 km * 1 km grid cell within 2 km of a modeled daily $PM_{2.5}$ exposure dataset (Kloog et al. 2014). Then, for each day during pregnancy as indicated by the clinical gestational age, the corresponding

$PM_{2.5}$ value was matched to each birth using statistical program R version 3.4.1 (R Core Team 2017). Finally, an average of $PM_{2.5}$ daily exposures for the entire pregnancy was taken to generate the average prenatal $PM_{2.5}$ exposure for each birth. $PM_{2.5}$ concentrations were from a prediction model uses satellite-derived aerosol optical depth measurements along with land use and meteorological variables to ascertain ground-level $PM_{2.5}$ concentrations. $PM_{2.5}$ measurements from two monitoring networks, US EPA Air Quality System and the Interagency Monitoring of Protected Visual Environments, were used to calibrate the model, which, in validation, performed consistently with an out-of-sample R^2 of 0.8 or higher. Further details on the prediction methodology are found in a previous publication (Kloog et al. 2014).

Covariates

In additional to birthweight, the Massachusetts Birth Registry records provides individual variables that are potential confounders in the relationship between $PM_{2.5}$ and birthweight. They include maternal age (years), maternal race (white, black, Asian, American Indian, other), maternal marital status (married, not married), maternal smoking (yes, no), maternal education (less than high school, high school, some college, college, advanced degree beyond college), parity (first-born, not first-born), maternal diabetes (yes, no), gestational diabetes (yes, no), maternal chronic high blood pressure (yes, no), maternal high blood pressure during pregnancy (yes, no), Kessner index of adequacy of prenatal care (adequate, intermediate, inadequate, no prenatal care) (Kessner et al. 1973), birth mode of delivery (vaginal, forceps, vacuum, first caesarian birth, repeat caesarian birth, vaginal birth after caesarian birth), year of birth (dummy variable for one of 2001 to 2013), clinical gestational age (weeks), newborn sex (male, female), and government support for prenatal care (yes, no). Birthweight was measured and recorded by medical staff at the time of birth; clinical gestational age was determined by a clinician who assessed the newborn's physical and neurologic maturity at birth or with an ultrasound during a prenatal care visit. Additionally, we performed analyses with adjustment for Census tract or block group percent black (%) and Census tract or block group median household income (1000s of US dollars per year). These data were based on the trailing 5-year estimate from the 2010 American Community Survey (U.S. Census Bureau 2017). We note that no covariates listed here are plausibly causal predictors of $PM_{2.5}$ exposure. Rather, variables such as maternal smoking may be surrogates for socioeconomic factors that predict both maternal smoking and neighborhood $PM_{2.5}$ exposure. Similar sets of covariates were used in recent studies investigating the $PM_{2.5}$ and birthweight (Ng et al. 2017; Rosa et al. 2017; Westergaard et al. 2017).

Statistical Modeling

As a first step, we estimated the average change in birthweight, adjusted for covariates, per $PM_{2.5}$ increase using linear regression. Secondly, we tested for effect modification by adding interactive terms between $PM_{2.5}$ and each of infant sex, maternal education, government support for prenatal care, median household income, and proportion of black population in Census tract or block group to assess effect modification. We then were compared estimated changes to birthweight, on average, to changes to birthweight at specific quantiles.

Quantile regression estimates the conditional quantile of the outcome (Koenker and Bassett 1978). In contrast to linear regression, which estimates the expected value of the outcome using the method of least squares, quantile regression relies on least absolute value regression and minimizes the sum of the absolute values of residuals, with weights for positive and negative residuals designed to target specific quantiles. The consequences of this difference in methods are that quantile regression does not assume normality in the distribution of errors, or constant variance, and that it is less susceptible to outliers than least squares regression. Further, the parameters of the covariates can differ across the quantiles. That is, there is no constraint requiring that the effect of e.g. maternal age on the median birthweight be the same as its effect on the e.g. 10th percentile of birthweight. In contrast, least squares regression assumes the effect of an exposure is to shift the entire distribution of birthweight without changing its shape. Specifically, we assumed that

$$Q_\tau(BW_i) = \alpha_\tau + \beta_{1,\tau}PM_i + \beta_{2,\tau}X_{2i} + \beta_{3,\tau}X_{3i} \dots + e_{i,\tau} \tag{1.1}$$

where Q_τ is the τ quantile of birthweight (BW), for infant i, given the $PM_{2.5}$ exposure (PM_i) and the set of covariates, X_{ni}. α_τ is the intercept and $e_{i,\tau}$ is the individual error term for the τ quantile. τ has a theoretical range of (0, 1). In this paper, we estimated the changes in the 1st through the 9th deciles, which correspond to the 10th, 20th, 30th … 90th percentiles of birthweight with quantile regression.

Results

We estimated the changes in birthweight on average, as well as at each birthweight decile, associated with an increase in prenatal $PM_{2.5}$ exposure. We also considered the possibility that the relationship between $PM_{2.5}$ and birthweight could be modified by individual SES or by neighborhood SES.

Table 1-1 provides descriptive statistics on the study population (n = 795,475). Overall, the mean birthweight was 3426 g and the mean $PM_{2.5}$ exposure was 10.1 $\mu g/m^3$ with an interquartile range (IQR) of 2.3 $\mu g/m^3$.

Table 1-1. Characteristics of Full-Term Singleton Births in Massachusetts from 2001 to 2013. Inclusion criteria were having complete maternal residence information, living within 2 km from a $PM_{2.5}$ prediction cell centroid, being a singleton, full-term (37 to 44 weeks of gestation), live birth weighing at least 500 g.

Variable	**Overall**
Total Births (n)	795475
Birthweight (g) (mean ± sd)	3425.72 ± 481.24
Average PM2.5 over entire Pregnancy (µg/m3) (mean ± sd)	10.12 ± 1.44
Clinical Gestational Age in Weeks (mean ± sd)	39.31 ± 1.17
Mother's Age in Years (mean ± sd)	30.15 ± 6.01
Census Tract Median Household Income ($1000s per year ± sd)	66.68 ± 28.26
Census Tract Black Population Proportion (± sd)	0.08 ± 0.14
Block Group Median Household Income ($1000s per year ± sd)	67.80 ± 32.85
Block Group Black Population Proportion (± sd)	0.08 ± 0.15
Newborn Female Sex (%)	49.06
Mother reported as Married (%)	69.04
Government Support for Prenatal Care (%)	32.86
Maternal Smoking (%)	13.64
Gestational Diabetes (%)	4.09
Other Diabetes (%)	0.86
High Blood Pressure during Pregnancy (%)	3.34
Chronic High Blood Pressure (%)	1.17
Parity: First-Born (%)	44.74
Mode of Delivery (%)	
vaginal	64.62
forceps	0.60
vacuum	3.55
first caesarian birth	17.51
repeat caesarian	12.19
vaginal birth after previous caesarean birth	1.52
Maternal Race (%)	
White	71.90
Black	8.53
Asian	7.60
American Indian	0.23
Other	11.74

Table 1-1 (Continued)

Variable	**Overall**
Kessner Index for Prenatal Care (%)	
adequate	78.55
intermediate	16.97
inadequate	3.29
no prenatal care	1.19
Maternal Education (%)	
Less than High School	10.68
High School	23.89
Some College	22.30
College	26.29
Advanced Degree	16.84

Higher exposure to $PM_{2.5}$ during pregnancy was associated with lower birthweight (Table 1-2). On average, being of higher gestational age, not the first-born, delivered with caesarian section, having adequate prenatal care, born to a mother who reported as married, more educated, was white, having gestational diabetes, other diabetes, or living in a Census block group with higher median household income were associated with higher birthweight while being female, born in later years of the study period, born to a mother who was older, smoking prior or during pregnancy, receiving government support for prenatal care, having chronic high blood pressure, high blood pressure during pregnancy, or living in a Census block group with higher black population proportion were associated with lower birthweights (Table 1-3). Figure 1-1 shows that maternal age, parity, smoking, clinical gestational age, and year of birth were strong sources of confounding. Omitting maternal race or parity from the model would have led to a more negative estimate of the association between $PM_{2.5}$ and birthweight while omitting smoking, clinical gestational age, or year of birth would have led to a more positive estimate of the association.

Table 1-2. Associations between $PM_{2.5}$ and Birthweight in Full-Term Live Singleton Births in Massachusetts from 2001 to 2013. The average change in birthweight per interquartile range (IQR) increase in $PM_{2.5}$ (2.3 $\mu g/m^3$) are shown.

		Estimated Change in Birthweight (g) per IQR increase in $PM_{2.5}$ and 95% Confidence Interval
On Average[1]		-16.38 (-18.98, -13.86)
At Specific Deciles of Birthweight		
	1st	-19.57 (-23.51, -15.67)
	2nd	-18.08 (-21.35, -14.86)
	3rd	-17.79 (-21.08, -14.61)
	4th	-16.89 (-19.89, -13.65)
	5th	-17.11 (-20.26, -14.01)
	6th	-16.19 (-19.19, -12.75)
	7th	-15.17 (-18.25, -11.67)
	8th	-16.56 (-20.31, -13.07)
	9th	-13.80 (-18.67, -8.79)

Table 1-3. Regression Coefficients from Full Model estimating Average Change in Birthweight per Unit Change in Covariates.

Variable	Estimated Average Change in Birthweight (g) and 95% Confidence Interval per Unit Increase or Change in Variable
Average $PM_{2.5}$ over entire Pregnancy	-7.37 (-8.53, -6.20)
Clinical Gestational Age	144.1 (143.26, 144.94)
Maternal Age	-0.20 (-0.41, 0.01)
Block Group Median Household Income ($1000s per year)	0.14 (0.10, 0.17)
Block Group Black Population Proportion	-40.27 (-47.79, -32.75)
Newborn Female Sex	-132 (-133.92, -130.08)
Mother reported as Married	34.33 (31.56, 37.11)
Government Support for Prenatal Care	-23.53 (-26.30, -20.76)
Smoking During or Prior to Pregnancy	-74.45 (-77.47, -71.43)
Gestational Diabetes	83.72 (78.79, 88.64)
Other Diabetes	136.56 (126.08, 147.04)
High Blood Pressure during Pregnancy	-54.13 (-63.10, -45.16)
Chronic High Blood Pressure	-39.82 (-45.19, -34.44)

Table 1-3 (Continued)

Variable	Estimated Average Change in Birthweight (g) and 95% Confidence Interval per Unit Increase or Change in Variable
Parity: Not First-Born	107.27 (104.98, 109.57)
Mode of Delivery (default = Vaginal)	
forceps	5.36 (-7.09, 17.80)
vacuum	-34.44 (-39.72, -29.15)
first caesarian birth	61.04 (58.32, 63.75)
repeat caesarian	67.46 (64.29, 70.62)
vaginal birth after previous caesarean birth	-13.09 (-21.01, -5.18)
Maternal Race (default = White)	
Black	-93.08 (-97.13, -89.03)
Asian	-167.65 (-171.38, -163.92)
American Indian	-71.02 (-90.96, -51.09)
Other	-54.15 (-57.58, -50.72)
Kessner Index for Prenatal Care (default = Adequate)	
intermediate	-30.08 (-32.71, -27.45)
inadequate	-41.01 (-46.47, -35.55)
no prenatal care	-10.20 (-19.15, -1.24)
Maternal Education (default = Less than High School)	
High School	22.96 (19.31, 26.62)
Some College	52.18 (48.26, 56.10)
College	53.14 (48.84, 57.44)
Advanced Degree	44.84 (40.17, 49.51)
Year of Birth (default = 2001)	
2002	-0.33 (-4.86, 4.21)
2003	4.99 (0.43, 9.56)
2004	2.09 (-2.58, 6.77)
2005	-8.02 (-12.67, -3.37)
2006	-15.69 (-20.35, -11.04)
2007	-16.79 (-21.81, -11.77)
2008	-8.42 (-13.12, -3.72)
2009	-22.11 (-27.32, -16.91)
2010	-33.62 (-39.47, -27.78)
2011	-38.36 (-45.54, -31.18)
2012	-43.47 (-49.42, -37.53)
2013	-48.67 (-54.89, -42.44)

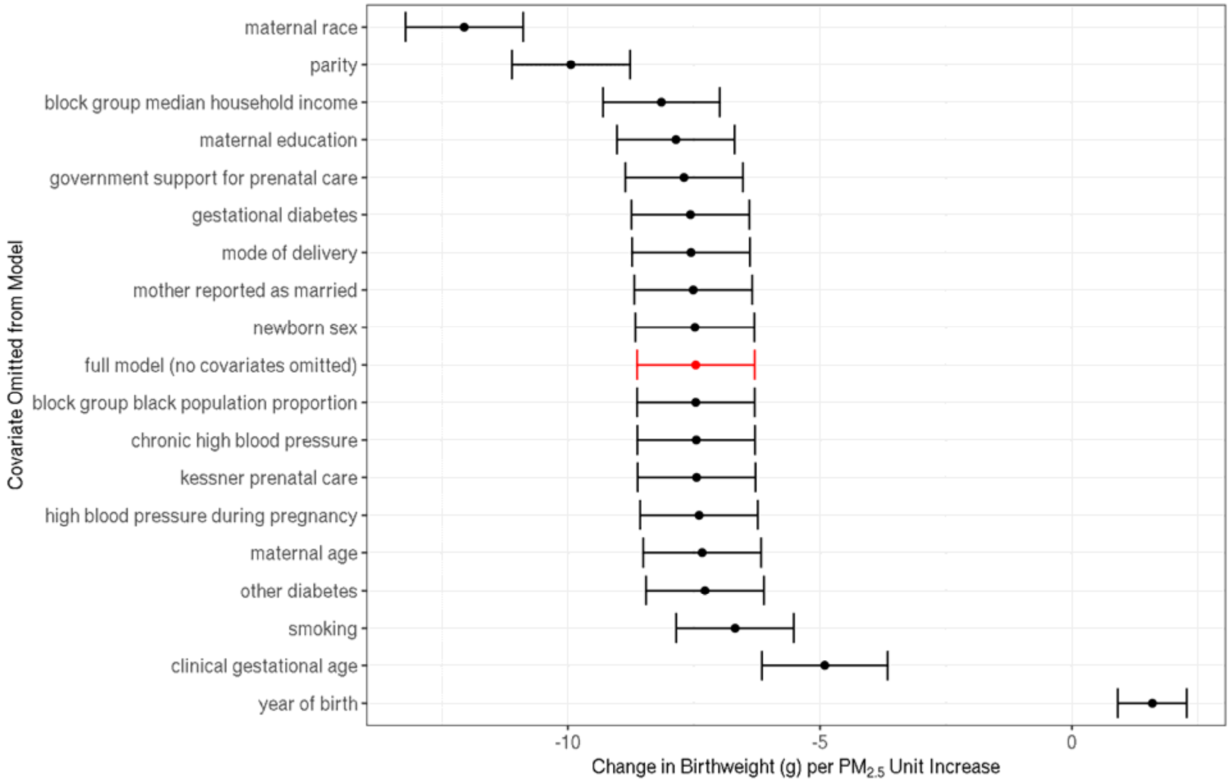

Figure 1-1. Assessment of Confounding by Regression Covariates. The estimated increase in birthweight per $\mu g/m^3$ increase $PM_{2.5}$ along with its 95% CI are shown in red for the full model and in black for each model when it omitted the covariate listed.

We did not find strong evidence for $PM_{2.5}$ effect modification by each of infant sex, maternal education, government support for prenatal care, median household income, and proportion of black population in Census tract or block group. Therefore, final models included main effects only. Likelihood-ratio tests found that the model that include Census block group median household income and black population proportion had the best fit compared to a model that uses Census tract variables and another that omits Census variables ($p < 0.05$). Thus, our final model included main effects of $PM_{2.5}$, individual covariates, and Census block group covariates.

Associations between $PM_{2.5}$ and birthweight were more negative at lower deciles of birthweight (Table 1-2; Figure 1-2). Figure 1-2 suggests that as birthweight decile increased, the negative association between $PM_{2.5}$ and change in birthweight moved closer to null. A test of linear trend for this relationship found that for each decile increase, the estimated change in birthweight increased by 4.06 g ($p < 0.05$). Compared to the average change in birthweight associated with an IQR increase in $PM_{2.5}$, the estimated changes to birthweight for the first through the fifth quantiles were more negative while the changes for the sixth, seventh, and ninth deciles were more positive. The most negative estimate was for the first decile of birthweight and the least negative was for the ninth decile.

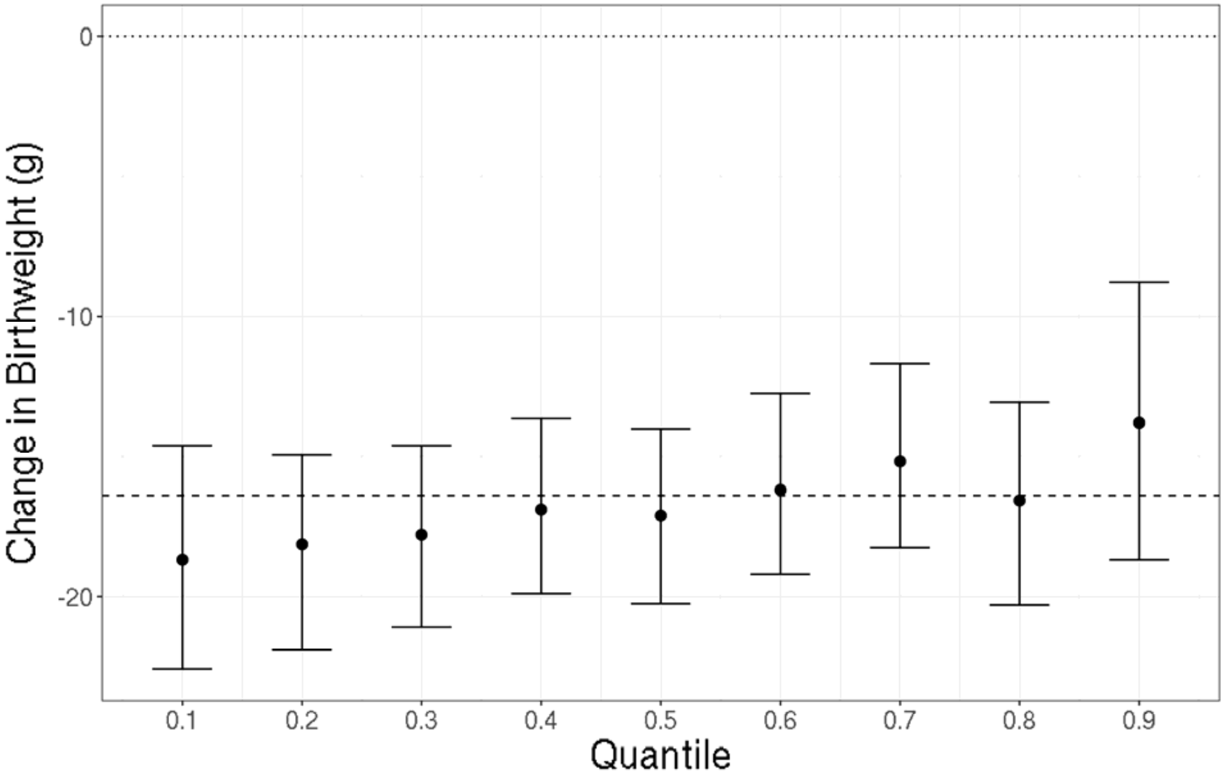

Figure 1-2. Associations between Interquartile Range Increase in $PM_{2.5}$ (2.3 $\mu g/m^3$) and Birthweight in Full-Term Live Singleton Births at Deciles of the Birthweight Distribution. Dotted line shows the average birthweight change, -16.38 g, associated with interquartile range increase in $PM_{2.5}$.

Discussion

Our analysis of full-term live singleton births in Massachusetts between 2001 and 2013 found a strong negative association between $PM_{2.5}$ exposure during pregnancy and birthweight. Applying quantile regression, we found that negative associations between $PM_{2.5}$ and birthweight were more severe for lighter newborns. This novel finding of an inequality suggests that there may be unmeasured factors influencing the negative association in the relationship between $PM_{2.5}$ and birthweight. Moreover, each gram reduction in birthweight may be more consequential for newborns in the lowest decile of birthweight, making the larger estimated association among the lightest newborns more concerning.

Negative associations between $PM_{2.5}$ and birthweight have previously been reported. The magnitude of the negative association from our analysis is on the higher end of the existing estimates (Sun et al. 2016). In contrast to some recent studies that found that the association between $PM_{2.5}$ and birthweight was modified by individual or community level SES (Erickson et al. 2016; Ng et al. 2017; Westergaard et al. 2017), we did not find strong evidence of effect modification in our analyses. These differences in findings compared to prior research could be due to differences in study population and methods.

Importantly, we found that the negative association between $PM_{2.5}$ and birthweight was larger in magnitude at the lower end of the birthweight distribution than those at the higher end. In other words, the negative association was estimated to be more severe for lighter newborns than for those who were heavier. Had the severity been equal, the estimated changes in birthweight at different deciles would have been closer together and an increasing linear trend between decile and change in birthweight would not have been observed (Table 1-2, Figure 1-2). Adding to this, our results imply that as $PM_{2.5}$ exposure increased, inequality in birthweight detriments between lighter and heavier newborns also increased. The difference in estimated birthweight detriments of $PM_{2.5}$ in a newborn in the lowest decile of birthweight versus one in the highest decile were larger when $PM_{2.5}$ exposures was higher. We are aware that there may be unmeasured factors that could have explained higher severity at the lower end of the birthweight distribution. Recently, disparities in environmental health have come to the forefront and there have been studies supporting that are factors other than $PM_{2.5}$ and commonly-used individual and community variables that can affect birth outcomes (Benmarhnia et al. 2017; Braveman et al. 2017; NIEHS 2017). Despite the inclusion of covariates that are related to SES on the individual and community level, there were differences in severity in the negative association between $PM_{2.5}$ and birthweight. These differences could potentially be explained by unmeasured variables and further research into this example of an environmental health disparity is warranted.

Our study had several strengths and limitations. We believe that the generalizability and statistical power were high. In addition to a large sample size of 775,768 compared to most prior analyses, we were able to assign $PM_{2.5}$ based on geocoded residential address and were not limited by postal code or census geographic levels of residential information (Erickson et al. 2016; Ng et al. 2017; Sun et al. 2016). Moreover, since the source of $PM_{2.5}$ exposure data had high temporal and spatial resolution as well as coverage, we minimized the number of people who needed to be excluded based on where they lived. This is in contrast to many prior studies, which relied on data from air monitors and thus had more limited spatial coverage (Basu et al. 2014; Brauer et al. 2008; Ebisu and Bell 2012; Ng et al. 2017). Moreover, using highly-resolved $PM_{2.5}$ minimized exposure misclassification as it better captured spatial and temporal variations. A criticism of our exposure assignment based on reported residential maternal address is that the residence was not an accurate representation of where a mother spent most of her time due to being in the workforce. However, we expect that the mothers to have spent more time at home than any place else, and air exchange rates in workplaces are usually considerably lower than in residences, limiting exposure to outdoor air pollution. Nevertheless, since most commutes and workplaces are in high-density urban areas, which tend to have higher $PM_{2.5}$ than lower-density residential areas, $PM_{2.5}$ assigned to each birth may be underestimated and the birthweight change associated with a unit $PM_{2.5}$ increase was biased away from the null. Another source of inaccurate location reporting is mothers moving residences during pregnancy, which we did not have information on. We expect the number of mothers who moved to be modest, but cannot quantify this. This moving should introduce classical exposure error into our exposure variable, biasing coefficients toward the null. Thus, inaccurate reporting of residential address is unlikely to have changed our finding of differential associations along the birthweight distribution. A further limitation, as in the case of most studies, was residual confounding. While we included many covariates in our regression analyses, we did not have information on some possible confounders such as body mass index.

Previous studies have shown that obese or underweight mothers are more likely to give birth to lighter newborns and that maternal obesity modifies the relationship between $PM_{2.5}$ and birthweight (Lakshmanan et al. 2015; Westergaard et al. 2017). Finally, although we further elucidated the relationship between $PM_{2.5}$ and birthweight with quantile regression, the exact mechanism of how $PM_{2.5}$ could lead to decreased birthweight remains unclear. Two major proposed pathways are inflammation and oxidative stress. Pulmonary inflammation stemming from $PM_{2.5}$ inhalation lead to poor gas exchange in the mother's lungs and consequently, low oxygen and nutrition exchange to the fetus, resulting in growth restriction and lower birthweight (Brook et al. 2010; Sun et al. 2016; Thayer and Kuzawa 2011). $PM_{2.5}$ is also thought to cause oxidative stress, which can lead to DNA damage in both the mother and fetus, hindering fetal growth. These two proposed mechanisms are difficult to test in epidemiological settings such as ours, which relied on birth certificate data and lacked biomarker data.

In full-term singleton live births in Massachusetts between 2001 and 2013, maternal exposure to $PM_{2.5}$ during pregnancy and birthweight was negatively associated with higher severity at lower quantiles of birthweight. We revealed the differences in associations by applying quantile regression, a seldom-used technique. Furthermore, we assigned exposure using $PM_{2.5}$ data that had high spatial and temporal resolution, which maximized statistical power, generalizability, and minimized exposure misclassification. Future work should seek to explain this environmental disparity between $PM_{2.5}$ and birthweight, perhaps by incorporating other determinants of health into analyses.

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Study 2. Evaluating Toxicities of Major Particulate Matter Constituents on Birthweight

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Abstract

Background: Maternal exposure to fine particulate air pollution ($PM_{2.5}$) during pregnancy has been linked to decreased newborn birthweight. Exposures leading to negative effects on birthweight are considered to be toxic since decreased birthweight is a risk factor for chronic disease. However, the toxicity of major constituents of $PM_{2.5}$ and how they compare to each other remain unclear.

Objective: We compare the estimated effect sizes of $PM_{2.5}$ constituents on birthweight compared to $PM_{2.5}$ and to each other to determine the relative toxicity of each constituent.

Methods: We estimated address-specific exposure to $PM_{2.5}$, elemental carbon (EC), organic carbon (OC), nitrate, and sulfate for each birth in Massachusetts from 2001 to 2012 using a calibrated chemical transport model. We estimated the effect sizes of each pollutant on continuous birthweight using multivariate regression.

Results: Compared to $PM_{2.5}$, EC were much more and nitrate was more toxic per unit mass while OC and sulfate were each slightly more toxic per unit mass in single constituent models that estimated the effect of a constituent with adjustment for total $PM_{2.5}$. When all constituents and total $PM_{2.5}$ were included in the same model, EC was most toxic, followed by nitrate, OC, and sulfate.

Conclusions: The relative toxicity of chemical constituents of $PM_{2.5}$ on continuous birthweight were different. EC was most toxic, followed by nitrate, OC, and sulfate.

Introduction

Maternal exposure to fine particulate air pollution, or particulate matter under 2.5 μm in aerodynamic diameter ($PM_{2.5}$), during pregnancy has been linked to lower birthweight (Basu et al. 2014; Dadvand et al. 2013; Ebisu and Bell 2012; Kloog et al. 2012; Stieb et al. 2012; Sun et al. 2016), and is a risk factor for cardiovascular disease, diabetes, obesity, respiratory conditions, and premature mortality (Belbasis et al. 2016; Boulet et al. 2011; Demerath et al. 2007; Hack et al. 1995; Korten et al. 2016; Reyes and Mañalich 2005). $PM_{2.5}$ can thus be considered to be toxic to human health. However, the majority of studies treated $PM_{2.5}$ as a homogenous exposure even though $PM_{2.5}$ is a mixture of particles with a varying size and chemical composition (Bell et al. 2010). Understanding the toxicity of different chemical constituents of $PM_{2.5}$ on birthweight is thus a research need and important for targeting air pollution control policy.

There have been few studies that estimated the toxicity of $PM_{2.5}$ chemical constituents on continuous birthweight (Sun et al. 2016). Existing analyses focused on estimating the effects between individual chemical constituents' mass concentrations and birthweight without concurrent adjustment for total $PM_{2.5}$ mass concentration (Bell et al. 2010; Darrow et al. 2011; Ebisu et al. 2014; Sun et al. 2016). While this approach leads to easily-interpretable results, it leads to estimates confounded by total $PM_{2.5}$ and by other constituents that covary with the individual constituent (Mostofsky et al. 2012). In this study, we instead estimate the effects between individual $PM_{2.5}$ constituents and birthweight with concurrent adjustment for total $PM_{2.5}$. Besides this difference in statistical modeling, we ascertained maternal exposure to $PM_{2.5}$ and constituents using output from a prediction model that uses chemical transport, meteorological, and land use data (Di et al. 2016). This contrasts with exposure assignment in most prior studies, which relied on measurements from monitoring networks and excluded births where the maternal residence was too far away from an air monitor, leading to losses in statistical power and potential selection bias (Basu et al. 2014; Bell et al. 2010; Darrow et al. 2011; Ebisu and Bell 2012). When predicted $PM_{2.5}$ and constituents were employed in prior studies (Laurent et al. 2014; Wilhelm et al. 2012), they used kriging or land use variables and did not incorporate chemical transport model output or meteorology, which are also predictive of pollution levels. For the chemical constituents in the present study, we selected elemental carbon (EC), organic carbon (OC), nitrate, and sulfate as they contribute to a majority of $PM_{2.5}$ (Di et al. 2016).

In summary, we estimated the effects of four $PM_{2.5}$ chemical constituents with concurrent adjustment for total $PM_{2.5}$ to assess their toxicity compared to $PM_{2.5}$. We also and other constituents, leading to a ranking of relative toxicity by each constituent on birthweight.

Methods

Study population

We obtained birth records from the Massachusetts Department of Public Health. The study base started with all births in Massachusetts from January 1, 2001 to December 31, 2012 (n = 907,766). In addition to birthweight, which was measured and recorded at the time of birth, the birth records contained information on maternal and individual characteristics. Consulting prior studies on the relationship between $PM_{2.5}$ and birthweight, and based on their potential to confound the relationship, we selected the following covariates *a priori* to include in out statistical modeling: maternal age (years), maternal race (white, black, Asian, American Indian, other), maternal marital status (married, not married), maternal smoking during or prior to pregnancy (yes, no), maternal education (highest level of education attained: less than high school, high school, some college,

college, advanced degree beyond college), parity (first-born, not first-born), maternal diabetes (yes, no), gestational diabetes (yes, no), maternal chronic high blood pressure (yes, no), maternal high blood pressure during pregnancy (yes, no), Kessner index of adequacy of prenatal care (adequate, intermediate, inadequate, no prenatal care) (Kessner et al. 1973), mode of delivery (vaginal, forceps, vacuum, first caesarian birth, repeat caesarian birth, vaginal birth after caesarian birth), clinical gestational age (weeks), year of birth (one of 2001 to 2012), season of birth (spring, summer, autumn, winter), newborn sex (male, female), and Medicaid-supported prenatal care (yes, no). In addition, we controlled for census block group level median household income and proportion of population that was black. Births missing address information (n = 23,093), with lower than a 500 g birthweight (n = 713), that were not live births (n = 8,155), nor singletons (n = 39,117), nor full-term (clinical gestational age between 37 and 44 weeks; n = 62,774) were excluded from analysis. We also excluded those with missing covariate data (n = 47,991), leading to a final sample size of 725,919. Our data usage was approved by the Massachusetts Department of Public Health and the human subjects committee at the Harvard T. H. Chan School of Public Health.

Exposure

We obtained predictions for $PM_{2.5}$ and four of its major constituents, EC, OC, nitrate, and sulfate from a model that incorporated outputs from the Goddard Earth Observing System Chemistry (GEOS-Chem) transport model in addition to meteorological and land use variables (Di et al. 2016). Briefly, GEOS-Chem outputs were combined with the meteorological and land use variables, and then calibrated to speciation monitoring data using a backward propagation neural network, which allows for complex and nonlinear associations between model inputs. This model was used to predict daily $PM_{2.5}$ and constituents mass concentrations at a 1 km * 1 km spatial resolution. Accuracy of the $PM_{2.5}$ and constituents prediction model were assessed using k-fold cross validation. The mean cross-validated R^2, computed for each year by regressing monitored $PM_{2.5}$ and constituents' values against predicted values then averaged, was 0.85, 0.71, 0.69, 0.83, and 0.81 for $PM_{2.5}$, EC, OC, nitrate, and sulfate, respectively.

Using the maternal residence information and reported clinical gestational age for each birth, we calculated average exposure to $PM_{2.5}$ and four of its major constituents, EC, OC, nitrate, and sulfate during the pregnancy. The address information was geocoded by the Massachusetts Department of Public Health against TomTom Multinet using AccuMail address and zip code as the input address field and zone. For each geocode, we identified the matching 1 km grid from the $PM_{2.5}$ and constituents data set. We then defined the entire pregnancy period as the relevant exposure window for each birth using the birthdate and clinical gestational age, which was determined by a clinician using ultrasound or physical examination during the latest prenatal visit or at birth. We averaged the daily $PM_{2.5}$ and constituents predictions in the 1 km grid of maternal residence for the entire duration of pregnancy to ascertain exposure for each birth.

Statistical Modeling

The goal of our statistical analysis was to determine the relative toxicities of the main constituents of $PM_{2.5}$ on birthweight. To do this, we built multivariate linear regression models to estimates the effects of each of the four constituents on continuous birthweight. We first sought to determine the association between a single constituent and birthweight with adjustment for $PM_{2.5}$:

$$(2.1) \qquad E(\text{Birthweight}) = \beta_0 + \beta_1(\text{constituent}) + \beta_2(PM_{2.5}) + [\gamma' X]$$

where the constituent was one of EC, OC, nitrate, and sulfate, and γ'X was the matrix of other model covariates. Inclusion of the constituent plus $PM_{2.5}$ is mathematically equivalent to modeling the modification of the $PM_{2.5}$ effect by the ratio of the constituent to $PM_{2.5}$:

$$(2.2) \qquad \beta_1(\text{constituent}/PM_{2.5})*(PM_{2.5}) + \beta_2(PM_{2.5}) = \beta_1(\text{constituent}) + \beta_2(PM_{2.5})$$

Therefore β_1 captures the incremental effect of a marginal increase in $PM_{2.5}$ exposure, given that it comes from the given constituent. A null association therefore means that the constituent is of average toxicity, not of no toxicity.

The relative contribution to confounding of each covariate is shown in Supplemental Figure 2-1; maternal race, parity, Census block group proportion of black population, Census block group median household income, maternal smoking, clinical gestational age, and year of birth were major sources of confounding in the negative association between $PM_{2.5}$ and birthweight. Although the multivariate models quantifying the associations of a single constituent with adjustment for $PM_{2.5}$ inform us of the relative toxicity of a constituent relative to $PM_{2.5}$, the effect estimates could be confounded by other constituents that covary with the single constituent (Mostofsky et al. 2012). Thus, we also determined the association between a constituent and birthweight with adjustment for other constituents and $PM_{2.5}$ in a multi-constituent linear regression model:

$$(2.3) \qquad \text{Birthweight} = \beta_0 + \beta_1(EC) + \beta_2(OC) + \beta_3(\text{nitrate}) + \beta_4(\text{sulfate}) + \beta_5(PM_{2.5}) + [\gamma'X]$$

We assessed the relative toxicity of each constituent on birthweight with this multi-constituent model that adjusts for $PM_{2.5}$ and other covariates. For this model, we scaled estimates to 1 $\mu g/m^3$ increases in each pollutant. As a sensitivity analysis and for comparison, we also scaled estimates to interquartile range (IQR) increases in each respective pollutant since pollutants had different levels and variances of mass concentrations.

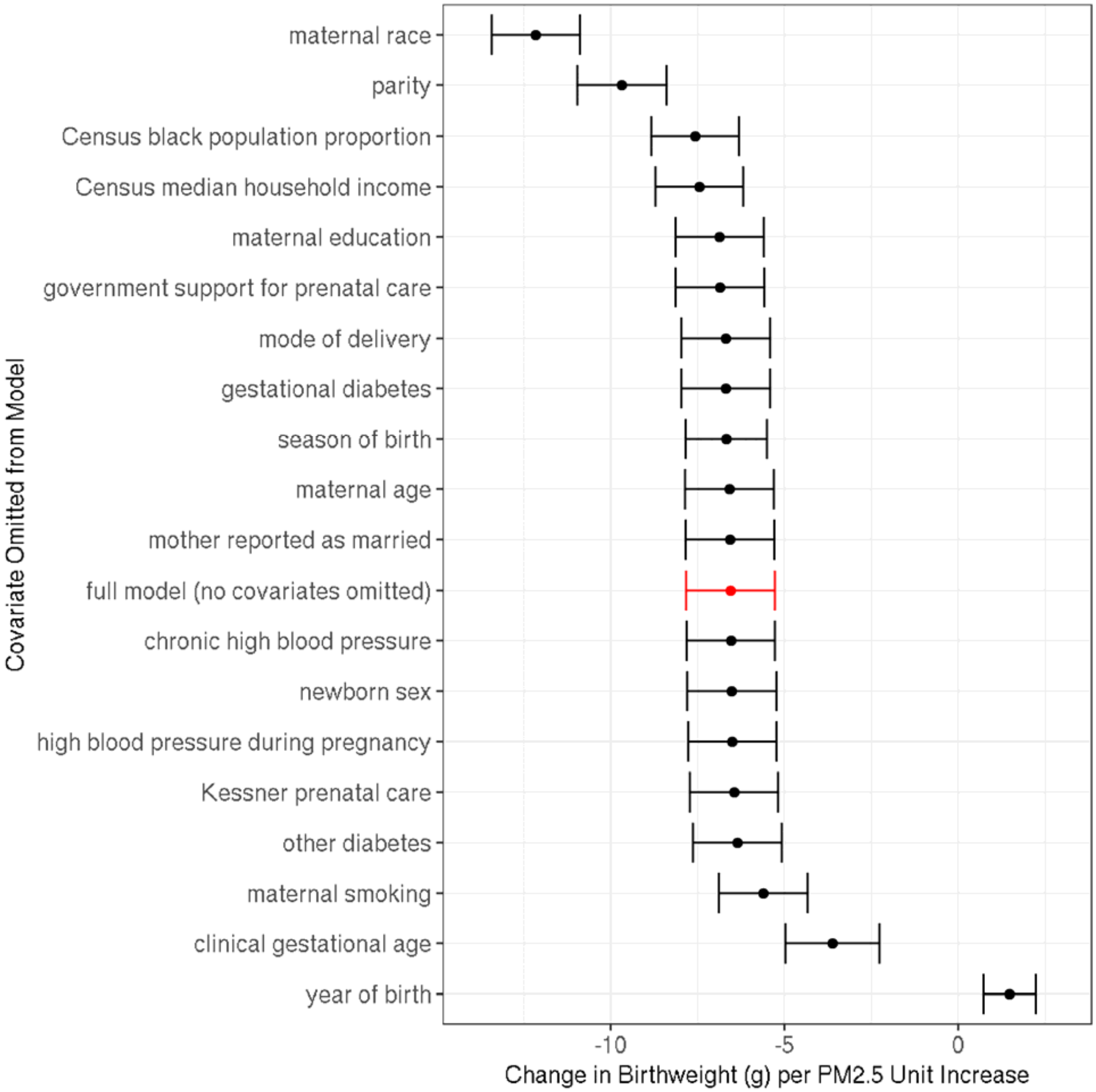

Figure 2-1. Assessment of Confounding by Covariates in the Relationship between Maternal Exposure to Particulate Matter under 2.5 µm in Aerodynamic Diameter ($PM_{2.5}$) during Pregnancy and Continuous Birthweight in Massachusetts from 2001 to 2012 (n = 725,919). Estimated changes in continuous birthweight along with the 95% confidence intervals are shown. The estimate for the full model is shown in red and the estimates for models omitting the covariate are in black.

Results

Table 2-1 summarizes the characteristics of the study population. The average maternal exposure to $PM_{2.5}$ over the entire pregnancy was 10.3 $\mu g/m^3$. EC, OC, nitrate, and sulfate accounted for about 70% of $PM_{2.5}$. Average exposures to OC and sulfate were highest, followed by nitrate and EC. Spearman correlations between $PM_{2.5}$ and its constituents are found in Table 2-2. Most $PM_{2.5}$ and constituents were moderately-associated with each other except between $PM_{2.5}$ and sulfate, which were strongly associated. More than two-thirds of mothers reported being married, less than a third received Medicaid support for prenatal care, and almost four-fifths were recorded as having received adequate prenatal care according to the Kessner index. Just over 70% of the mothers were white and almost 90% had at least a high school education. Consistent with prior literature, maternal exposure to $PM_{2.5}$ during pregnancy was negatively associated with birthweight after adjustment for covariates: per 1 $\mu g/m^3$ increase in $PM_{2.5}$, newborns were 7 (95% CI: 5, 8) g lighter on average.

Table 2-1. Characteristics of Full-Term Live Singleton Births in Massachusetts from 2001 to 2012 (n = 725,919).

Variable	Overall
Continuous Variables (mean ± interquartile range (IQR))	
Average Particulate Matter under 2.5 µm in diameter ($PM_{2.5}$) ($\mu g/m^3$)	10.3 ± 2.0
Average Elemental Carbon (EC) ($\mu g/m^3$)	0.5 ± 0.2
Average Organic Carbon (OC) ($\mu g/m^3$)	2.8 ± 1.4
Average Nitrate ($\mu g/m^3$)	1.2 ± 0.5
Average Sulfate ($\mu g/m^3$)	2.8 ± 1.5
Birthweight (g)	3442 ± 624
Clinical Gestational Age (weeks)	39.3 ± 1.0
Maternal Age (years)	30.1 ± 8.6
Median Household Income at Census Block Group (10,000 USD/year)	6.77 ± 4.24
Proportion Black Population at Census Block Group	0.08 ± 0.08

Table 2-1 (Continued)

Variable	**Overall**
Binary and Categorical Variables (%)	
Newborn Sex = Female	49.02
Parity: First-Born	45.2
Mother Married	69.04
Medicaid Support for Prenatal Care	32.64
Maternal Smoking	13.97
Gestational Diabetes	3.95
Other Diabetes	0.86
High Blood Pressure during Pregnancy	3.19
Chronic High Blood Pressure	1.15
Season of Birth	
Winter	24.45
Spring	25.18
Summer	26.00
Fall	24.37
Mode of Delivery	
Vaginal	65.51
Forceps	0.61
Vacuum	3.61
First caesarian birth	16.78
Repeat caesarian	11.97
Vaginal birth after previous caesarean birth	1.52
Maternal Race	
White	71.52
Black	8.23
Asian	7.53
American Indian	0.22
Other	12.5
Kessner Index for Prenatal Care	
Adequate	78.78
Intermediate	17.05
Inadequate	3.29
No Prenatal Care	0.87
Maternal Education	
Less than High School	10.8
High School	24.52
Some College	22.02
College	26.36
Advanced Degree	16.29

Table 2-2. Spearman Correlation Coefficients between Average Maternal Exposures to $PM_{2.5}$ and Constituents during Pregnancy in Massachusetts from 2001 to 2012 (n = 725,919).

	$PM_{2.5}$	**EC**	**OC**	**Nitrate**	**Sulfate**
$PM_{2.5}$	1				
EC	0.44	1			
OC	0.59	0.55	1		
Nitrate	0.39	0.32	0.49	1	
Sulfate	0.72	0.35	0.46	0.38	1

Figure 2-2 illustrates the associations between a constituent and continuous birthweight with adjustment for $PM_{2.5}$. The estimated incremental birthweight change associated with a 1 $\mu g/m^3$ increase in each of the components compared to a generic mixture of $PM_{2.5}$ was negative for all four components, suggesting that all four decrease birthweight by more than average, and therefore than the remaining 30% of $PM_{2.5}$ mass. The estimated EC effect was much larger in magnitude than the estimated birthweight decrease associated with an average $\mu g/m^3$ increase in $PM_{2.5}$ (Figure 2-2: leftmost pane). In other words, the estimated decrease in birthweight with increased exposure to $PM_{2.5}$ was larger if the exposure was comprised mostly of EC than of other $PM_{2.5}$ constituents. We observe a similar pattern of associations for nitrate but the difference in magnitude was smaller. The incremental birthweight decrease associated in an increase in OC and sulfate were considerably smaller.

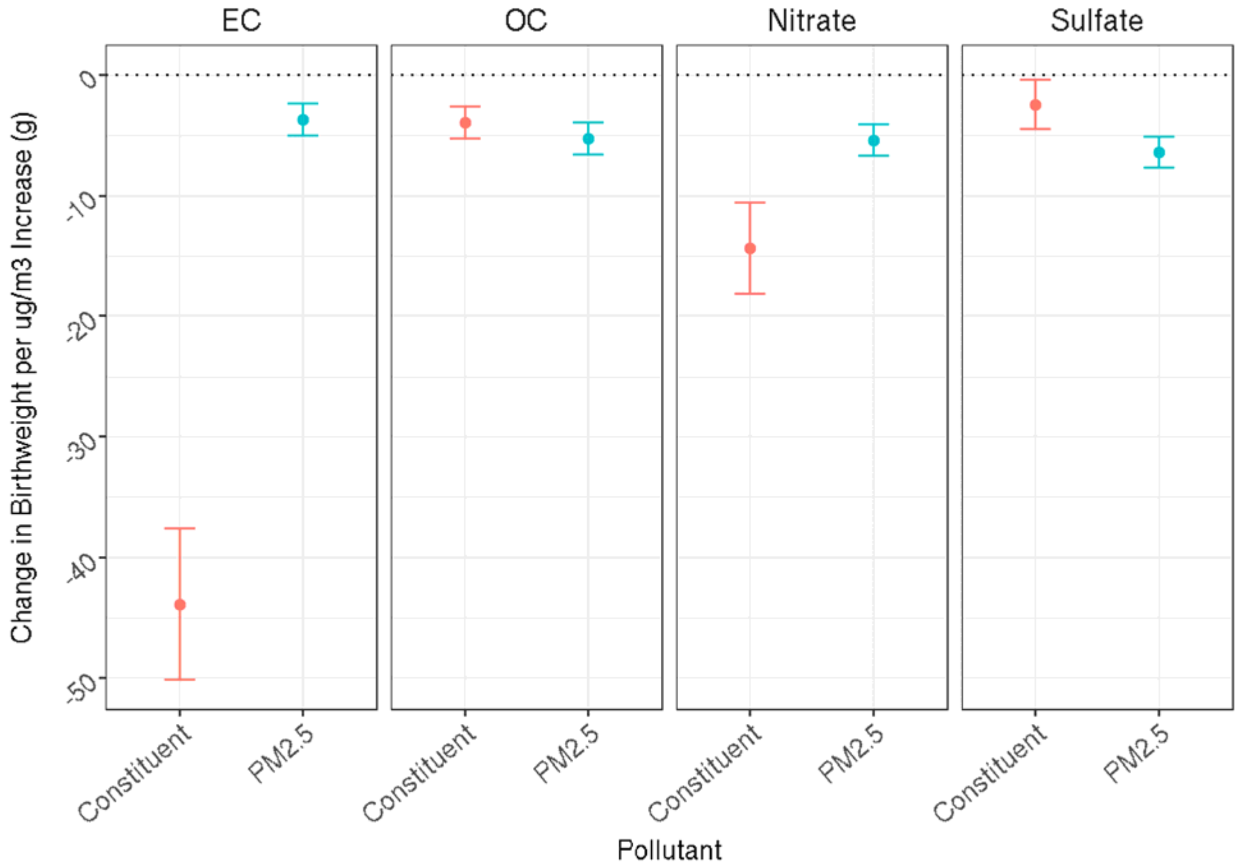

Figure 2-2. Estimated Change in Birthweight per 1 µg/m^3 increase in a PM$_{2.5}$ Constituent adjusted for PM$_{2.5}$ in Massachusetts from 2001 to 2012 (n = 725,919). PM$_{2.5}$ constituents include elemental carbon (EC), organic carbon (OC), nitrate, and sulfate. Point estimate and 95% confidence interval per individual constituent are in red while those for PM$_{2.5}$ are in blue. Four separate linear models for each of the four constituents were run and included adjustment for PM$_{2.5}$ and covariates.

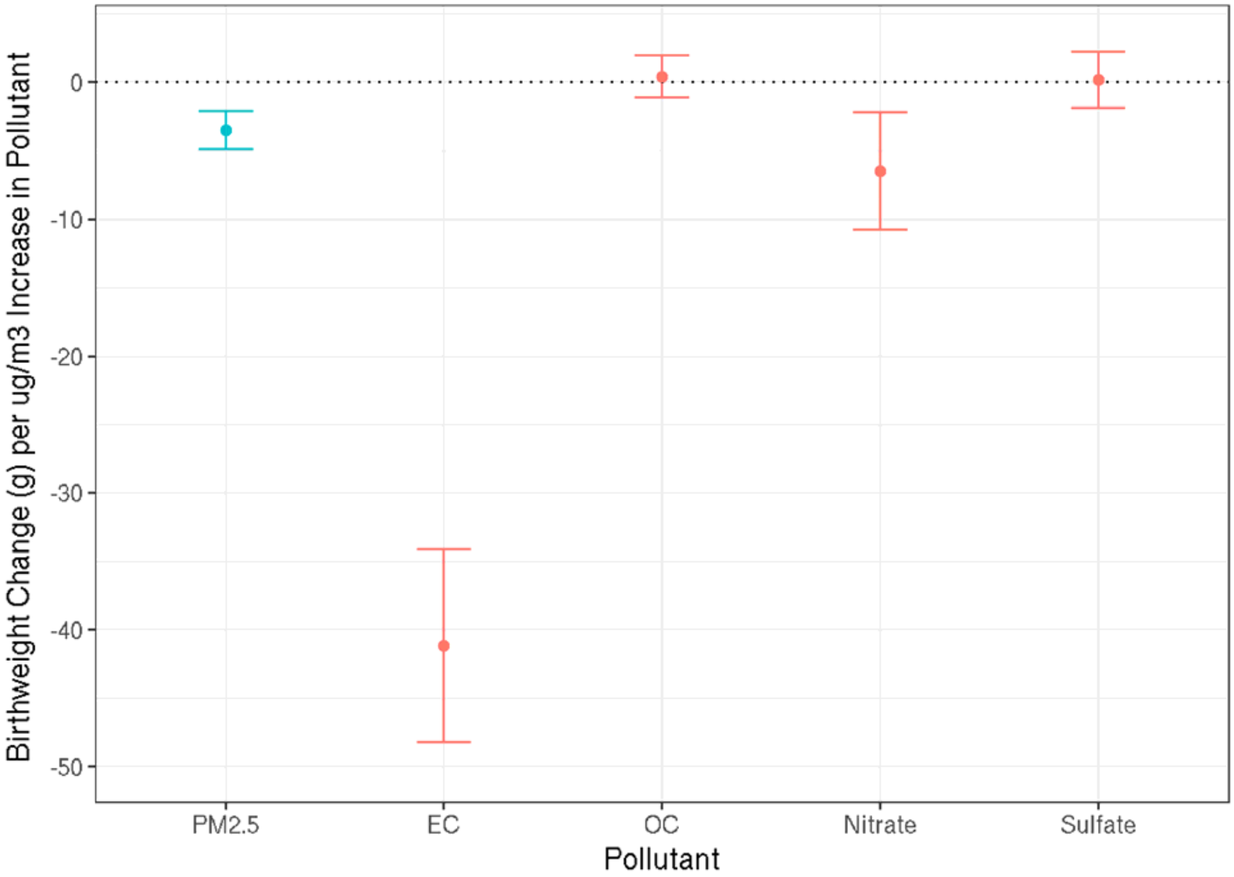

Figure 2-3. Estimated Change to Birthweight per 1 µg/m^3 increase in PM$_{2.5}$, EC, OC, Nitrate, and Sulfate in Massachusetts from 2001 to 2012 (n = 725,919). Point estimate and 95% confidence interval per individual constituent are in red while that per PM$_{2.5}$ is in blue. A single multi-constituent linear regression with the four constituents and PM$_{2.5}$ was run.

While Figure 2-2 illustrates the relative toxicities of a constituent compared to total $PM_{2.5}$ one at a time, Figure 2-3 shows the toxicity of a constituent with simultaneous adjustment for $PM_{2.5}$ and other constituents. An increase in total $PM_{2.5}$ was associated with a decrease in birthweight and the effect size was much larger if the increase was due to EC. Nitrate particles also showed greater effects per $\mu g/m^3$, while in the fully adjusted model OC and sulfate particles showed average toxicity, with no incremental effect above that of $PM_{2.5}$ on average.

Discussion

In a large cohort of full-term singleton live births in Massachusetts from 2001 to 2012, we found that maternal exposure to $PM_{2.5}$ during pregnancy was negatively associated with birthweight. Furthermore, the relative toxicities of four major $PM_{2.5}$ constituents, EC, OC, nitrate, and sulfate, on birthweight compared to $PM_{2.5}$ and to each other were different. While the negative association between $PM_{2.5}$ and continuous birthweight is well-established, the relative impacts of $PM_{2.5}$ chemical constituents compared to a $PM_{2.5}$ mixture are less understood (Stieb et al. 2012; Sun et al. 2016). From our comparison of relative toxicities of each constituent on birthweight, we found that the toxicity of EC was the greatest, followed by nitrate particles. OC and sulfate particles appeared to have average toxicity. Presumably, the constituents that make up the other 30% of $PM_{2.5}$ have lower than average toxicity. Interestingly, the two most toxic constituents derived primarily from traffic emissions, which are local sources. This indicates that control of traffic-derived particles could be an effective strategy for reducing detrimental effects of $PM_{2.5}$ on fetal growth. While the United States Environmental Protection Agency (EPA) is responsible for general emission standards for vehicles, there is considerable room for local action to reduce traffic through strategies such as zoning, limiting personal vehicles, and increased mass transit.

Since each pollutant had different ranges and variances, we conducted a sensitivity analysis with estimates scaled to an IQR increase in each respective pollutant. Evaluating the associations per IQR increases in each pollutant no longer leads to comparisons standardized to a mass concentration change but comparisons standardized to the difference in exposures between mothers in the most and the least exposed quartiles. Even with IQR scaling, EC exhibited the strongest negative associations with birthweight (Figures 2-4 and 2-5). When all constituents and total $PM_{2.5}$ were included in the same model, the ranking of toxicities between constituents and birthweight remained the same with EC, nitrate, then sulfate and OC (Figure 2-5). The much stronger toxicity of EC was less pronounced with IQR scaling. Although the exposure assignment and statistical methods used were different, a recent meta-analysis found that EC, OC, and nitrate were negatively associated with birthweight, and that the association was strongest for EC (Sun et al. 2016). Similar to our findings, the association between sulfate and birthweight was weak.

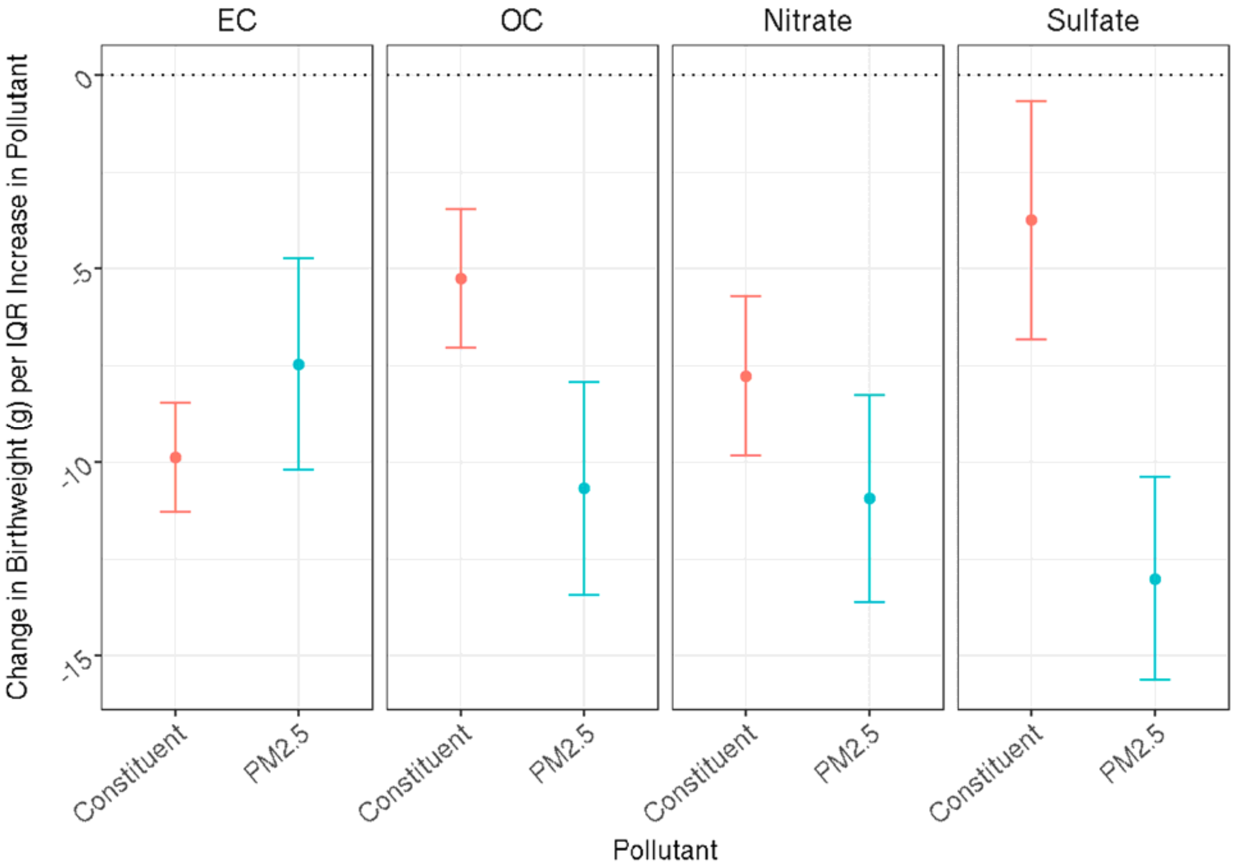

Figure 2-4. Estimated Change in Birthweight per Interquartile Range (IQR) increase in a $PM_{2.5}$ Constituent adjusted for $PM_{2.5}$ in Massachusetts from 2001 to 2012 (n = 725,919). $PM_{2.5}$ constituents include elemental carbon (EC), organic carbon (OC), nitrate, and sulfate. Point estimate and 95% confidence interval per individual constituent are in red while those for $PM_{2.5}$ are in blue. Four separate linear models for each of the four constituents were run and included adjustment for $PM_{2.5}$ and covariates. IQRs ($\mu g/m^3$): $PM_{2.5}$ = 2.0, EC = 0.2, OC = 1.4, Nitrate = 0.5, Sulfate = 1.5.

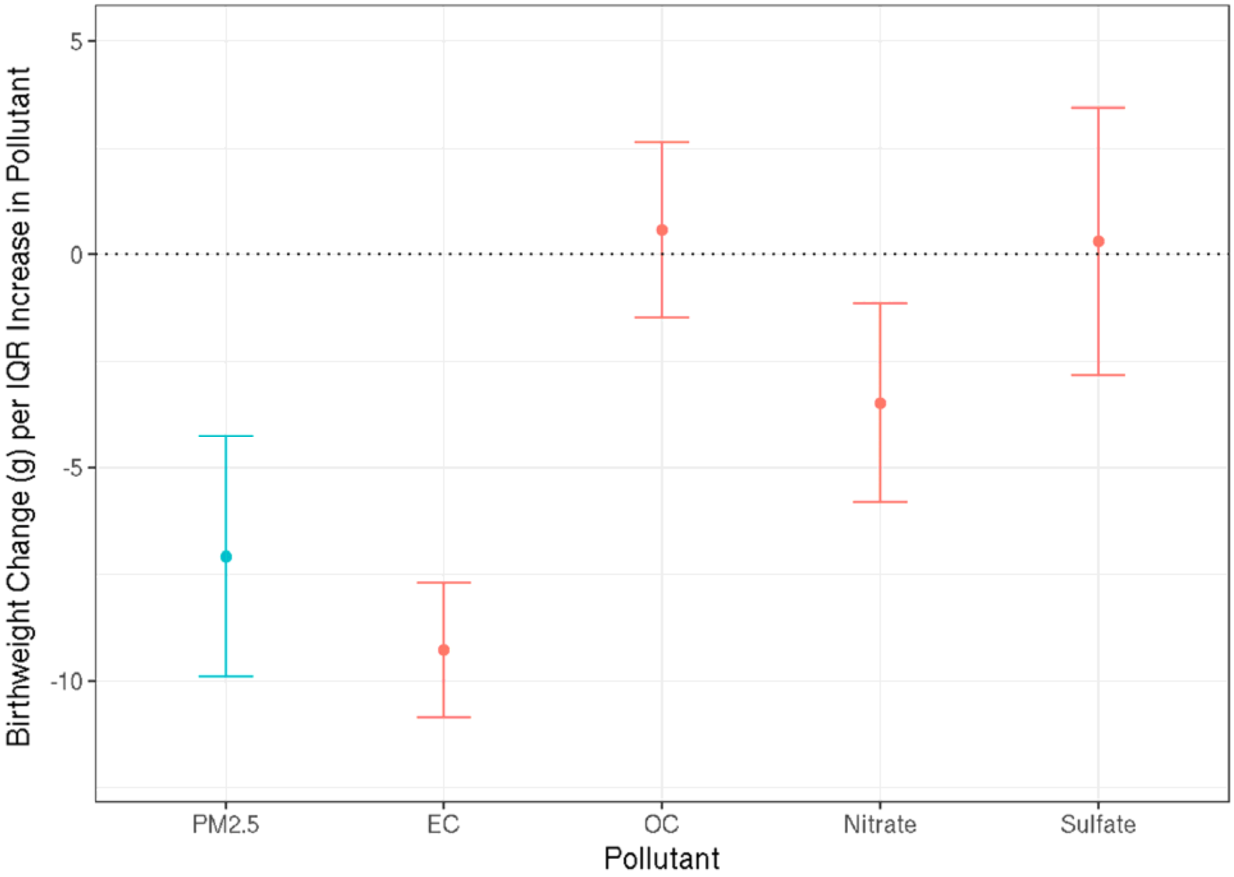

Figure 2-5. Estimated Change to Birthweight per Interquartile Range (IQR) increase in $PM_{2.5}$, EC, OC, Nitrate, and Sulfate. $PM_{2.5}$ constituents include elemental carbon (EC), organic carbon (OC), nitrate, and sulfate in Massachusetts from 2001 to 2012 (n = 725,919). Point estimate and 95% confidence interval per individual constituent are in red while that per $PM_{2.5}$ is in blue. A single multi-constituent linear regression with the four constituents and $PM_{2.5}$ was run. IQRs ($\mu g/m^3$): $PM_{2.5}$ = 2.0, EC = 0.2, OC = 1.4, Nitrate = 0.5, Sulfate = 1.5.

Differences in relative toxicities of the constituents were expected given the proposed mechanisms of how maternal exposure to air pollution affect birthweight. $PM_{2.5}$ is thought to lead to pulmonary inflammation and impair gas exchange in the lungs (Sun et al. 2016). This in turn lowers maternal blood oxygen circulation and limits availability of oxygen to the fetus, inhibiting fetal growth. Since different constituents of $PM_{2.5}$ have different chemical properties, they can also interact differently with maternal lung tissue and have varying inflammatory potentials. Another mechanism through which $PM_{2.5}$ is thought to impact birthweight is oxidative stress, which leads to DNA damage. Since the different chemical constituents of $PM_{2.5}$ have different oxidative potentials, they could also have different propensities to cause DNA damage and affect the growing fetus to differing degrees. Although the inflammatory and oxidative stress mechanisms through which maternal exposure to $PM_{2.5}$ affect the growing fetus are unconfirmed, it is highly plausible that different chemical constituents of $PM_{2.5}$ would have different consequences on birthweight given current understanding of biological systems. The evidence from the current study and from prior epidemiological studies support this claim.

Our study had strengths and limitations. First, we applied an appropriate statistical modeling strategy to assess the relative toxicities of $PM_{2.5}$ constituents. Prior studies assessed the association between a constituent and birthweight without adjustment for total $PM_{2.5}$ (Bell et al. 2010; Darrow et al. 2011; Ebisu et al. 2014; Sun et al. 2016), which meant that the estimates were confounded by total $PM_{2.5}$ and by other constituents with high correlation to the single constituent in the model (Mostofsky et al. 2012). The single constituent models adjusted for total $PM_{2.5}$ to limit confounding from total $PM_{2.5}$ and the multi-constituent model additionally limited confounding from other constituents. The current study also had a large sample size with a relatively small number of births excluded due to missing exposure data. In prior studies, births would be excluded when the maternal residence was too far away from an air monitor. In the current study, which uses predictions from an exposure model, we were able to match every birth to an area for which daily predictions for $PM_{2.5}$ and its constituents were made. Importantly, the predictions of $PM_{2.5}$ and its constituents were created for use in epidemiological studies and they have recently been used for understanding the relationship between $PM_{2.5}$, its constituents, and epigenetics (Nwanaji-Enwerem et al. 2017a, 2017b; Peng et al. 2017). There remained limitations in the exposure assignment in our study. Although EC, OC, nitrate, and sulfate make up the majority of total $PM_{2.5}$, other constituents such as metals were not considered. Metals have previously been associated with decreased birthweight and are known to persist in fetal tissues and have long-term health consequences (Bell et al. 2010; Sun et al. 2016). Thus, the relative impacts by each constituent on birthweight (Figure 2), could change with the inclusion of remaining $PM_{2.5}$ constituents but we do not expect the ranking of relative toxicities of the four major $PM_{2.5}$ constituents to change. Another issue with our exposure assignment was exclusion due to missingness in maternal residential information and other covariates. Less than 10% were excluded due to missingness and we do not believe that exposures are strongly associated with missingness. Thus, we expect this bias from missing maternal residence and covariate data to be non-differential. But there remained the potential that the reported maternal residence did not accurately reflect the maternal location during pregnancy. Potential inaccurate reporting was unavoidable and unmeasured but behaviors such as spending time at work, away from the maternal residence, would likely have resulted in biases away the null if the work environments were located in more urban areas compared to residential areas. Finally, our study suffered from unmeasured confounding and measurement error as well as misclassification in the outcome. With the many potential sources of confounding adjusted for in our statistical analysis and the ubiquity of the birthweight measurement, we expected the biases from these factors to be minimal. The generalizability of our results is also limited to study bases that are similar to births in Massachusetts from 2001 to 2012, with similar demographics and exposure profiles.

Maternal exposure to $PM_{2.5}$ during pregnancy was negatively associated with birthweight and the relative impacts of four major constituents, EC, OC, nitrate, and sulfate, were markedly different. EC was most impactful, followed by nitrate, then OC and sulfate with similar impacts. Our results were not confounded by total $PM_{2.5}$, which was adjusted for in our statistical analysis. As birthweight is an important predictor for health over the life course for newborns, our findings can inform air pollution control policy to maximize health benefits.

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Study 3. Residential Greenness and Birthweight in Massachusetts: Nonlinearity and Effect Modification by Socioeconomic Status

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Abstract

Background: Residential greenness may increase opportunities for physical activity, social engagement and psychological restoration, as well as potentially decrease exposure to air pollution, noise, and extreme temperatures. Thus, greenness during pregnancy may benefit maternal health and the newborn's birthweight.

Objectives: We investigated the associations between maternal exposure to residential greenness and birthweight as well as potential nonlinearity and effect modification by socioeconomic status (SES) in Massachusetts between 2001 and 2013.

Methods: Greenness during pregnancy was measured with normalized difference vegetation index (NDVI). We estimated average changes in continuous birthweight, odds of being low birthweight (LBW: < 2500 grams) or small for gestational age (SGA: < 10th percentile of birthweight stratified by sex and gestational age) per increase in greenness, adjusted for individual and neighborhood covariates. Nonlinearity was assessed by incorporating a spline for NDVI.

Results: Increased exposure to greenness during pregnancy was associated with higher birthweights and lower odds of LBW or SGA. The relationship between greenness and birthweight was nonlinear. On average, between 0.25 and 0.50 NDVI, an IQR increase in NDVI (0.22) was associated with a 17.01 (95% CI: 13.63, 20.38) g increase in birthweight; between 0.50 and 0.75 NDVI, the association was 7.61 (2.93, 12.29) g. There was effect modification between greenness and odds of LBW and SGA. The strongest negative associations were found in those born to better-educated mothers (LBW, SGA), those without government assistance for prenatal care (SGA), and those living in higher median household income areas (SGA).

Conclusions: Greenness exposure during pregnancy was associated with increased birthweights and decreased odds of LBW and SGA. The positive association between greenness and continuous birthweight was stronger in the lower range of NDVI. Between greenness and odds for LBW and SGA, the association was more strongly negative among those of higher SES.

Introduction

Decreased birthweights are associated with significantly higher risks for cardiovascular and respiratory disease, diabetes, obesity, and premature mortality (Belbasis et al. 2016; Boulet et al. 2011; Hack et al. 1995; Korten et al. 2016; Reyes and Mañalich 2005). A multitude of environmental exposures has previously been found to be associated with lower birthweight: high ambient air temperature, air pollution such as particulate matter, ozone, and nitrogen dioxide, as well as heavy metals, chemicals in second hand smoke, and endocrine disruptors (Arroyo et al. 2016; Etzel et al. 2017; Kloog et al. 2012; Luo et al. 2017; Sun et al. 2016; Yang et al. 2017). Understanding the environment factors associated with birthweight can lead to actionable policy to improve health of newborns from birth to adulthood.

Recently, there has been growing interest in how residential greenness may affect birthweight (Abelt and McLafferty 2017; Casey et al. 2016; Cusack et al. 2017a; Dadvand et al. 2012, 2013; Ebisu et al. 2016; Hystad et al. 2014). Most prior studies found that increased maternal exposure to greenness is positively associated with birthweight. Greenness around the maternal residence is thought to improve health through mitigating the detriments from environmental exposures, restoring mental health, and promoting healthy behaviors (Markevych et al. 2017). Vegetation, especially trees, help buffer and reduce exposure to air pollution, noise, and heat (Gidlöf-Gunnarsson and Öhrström 2007; Lafortezza et al. 2009; Nowak et al. 2006; Oliveira and Epiphanio 2012). Contact with greenness has also been shown to relieve stress and mental fatigue (Frumkin et al. 2017; Hartig et al. 2014). Higher residential greenness often indicates increased access to recreational space and is associated with healthy behaviors such as physical activity and social contact (Bowler et al. 2010; Frumkin et al. 2017; McMorris et al. 2015; Richardson et al. 2013). Through these pathways, higher residential greenness can improve maternal health during pregnancy, which, as a consequence, leads to a healthy fetal environment and a newborn of normal birthweight.

There remains gaps in understanding the relationship between residential greenness and birthweight. Although most prior studies showed positive associations between greenness and higher birthweights (Banay et al. 2017), a few found null or negative associations (Abelt and McLafferty 2017; Cusack et al. 2017b). The results from one recent study showed a positive association in Portland, Oregon, but a negative association in Austin, Texas, suggesting that there may be variation in how greenness is related to birthweights due to differences in vegetation (Cusack et al. 2017b). Thus, it is important to investigate these associations in additional study settings.

We therefore investigate the relationship between residential greenness and birthweight among all births in Massachusetts from 2001 to 2013. To gain a better understanding of this relationship, we assess possible nonlinear relationships by using a spline for greenness. We also consider effect modification by socioeconomic status (SES) as consensus on how indicators of SES, such as maternal education, modify the association between greenness and health has not been reached (Banay et al. 2017; James et al. 2015).

Methods

Study population

We used data from the Massachusetts Birth Registry from January 1, 2001 to December 31, 2013 (n = 978,225). We excluded records that had missing residence information (n = 23,943), those that were not live births (n = 8,621), not singletons (n = 42,186), not full-term (< 37 weeks; n = 77,036), and below 500 g in birthweight (n = 772). A further 45,232 were excluded due to missing covariate data, leading to a final sample size of 780,435. Similar exclusion criteria were applied in recent studies (Abelt and McLafferty 2017; Casey et al. 2016; Cusack et al. 2017a). Births with maternal residence information were geocoded by the Massachusetts Department of Public Health against TomTom Multinet using AccuMail address and zipcode as the input address field and zone. The use of birth data was approved by the Massachusetts Department of Public Health and the human subjects committee at the Harvard T. H. Chan School of Public Health.

Exposure: Residential Greenness

To assess residential greenness, we used remote sensing data from the Moderate-resolution Imaging Spectroradiometer (MODIS) aboard the Terra and Aqua satellites operated by the United States National Aeronautics and Space Administration. We derived the normalized difference vegetation index (NDVI) from these data (Weier and Herring 2000). Chlorophyll in plant leaves absorbs visible light between 0.4 and 0.7 μm in wavelength for photosynthesis, while leaves reflect near-infrared light (0.7-1.1 μm). NDVI calculates a ratio of difference between visible and near-infrared divided by the sum of visible and near-infrared light to estimate the quantity of vegetation in a given area. MODIS provides NDVI at 250 m resolution. Higher NDVI values are indicative of more vegetation, and thus higher greenness.

For each birth, we assigned an average NDVI value, referred to as “greenness,” representative of the maternal residential greenness exposure during pregnancy. First, using the geocodes of each birth, we determined the 250 m by 250 m grid pixel in which the mother reported to have resided at the time of the birth. We chose 250 m as the spatial resolution since it captures the local residential greenness outside the mother’s home and is most accessible (Cusack et al. 2017a). After the grid pixel of each birth was determined, we determined, again for each birth, the exposure window as time during which each mother was pregnant using the clinical gestational age reported in the birth record. We then calculated the average of NDVI values occurring during the pregnancy for each birth from a time-varying NDVI dataset containing measurements from January, April, July, and October representing winter, spring, summer, and fall. This exposure assignment is similar to those used in recent studies (Casey et al. 2016; Cusack et al. 2017a). For the births in our analysis, greenness ranged from -0.14 to 0.93 with an interquartile range (IQR) of 0.22.

Outcomes

Birthweight measured at the time of birth in grams was the primary outcome. We also defined low birthweight (LBW), birthweight less than 2,500 g, and small for gestational age (SGA), birthweight below the 10th percentile of the birthweights for the newborn's sex and gestational age. Gestational age was determined by clinical examination or by ultrasound by a medical professional at the latest prenatal visit or at birth.

Covariates

Model covariates were chosen a priori and selected for their potential to confound the relationship between exposure to greenness and birthweight. They include maternal age (years), maternal race (white, black, Asian, American Indian, other), maternal marital status (married, not married), maternal smoking prior to or during pregnancy (yes, no), maternal education (highest level of education attained: less than high school, high school, some college, college, advanced degree beyond college), parity (first-born, not first-born), maternal diabetes (yes, no), gestational diabetes (yes, no), maternal chronic high blood pressure (yes, no), maternal high blood pressure during pregnancy (yes, no), Kessner index of adequacy of prenatal care (adequate, intermediate, inadequate, no prenatal care) (Kessner et al. 1973), birth mode of delivery (vaginal, forceps, vacuum, first caesarian birth, repeat caesarian birth, vaginal birth after caesarian birth), clinical gestational age (weeks), year of birth (one of 2001 to 2013), newborn sex (male, female), and government support for prenatal care (yes, no). Season of birth (spring: birth date between March 21 and June 20, summer: June 21 to September 20, autumn: September 21 to December 20, winter: December 21 to March 20), Five-year estimates of Census black population proportion and Census median household income (10,000s of US dollars per year) from the 2010 Census at the block group level were also included (U.S. Census Bureau 2017). Finally, we included particulate air pollution under 2.5 μm in diameter ($PM_{2.5}$) since maternal exposure to $PM_{2.5}$ during pregnancy is negatively associated with birthweight (Bell et al. 2010; Dadvand et al. 2013; Darrow et al. 2011; Kloog et al. 2012; Stieb et al. 2012; Sun et al. 2016). Each birth's $PM_{2.5}$ exposure was calculated by averaging daily $PM_{2.5}$ predictions of the 1 * 1 km grid pixel of the maternal residential address during the entire pregnancy. The $PM_{2.5}$ data were from a hybrid prediction model that used satellite-derived aerosol optical depth and performed consistently with an out-of-sample R^2 above 0.8 (Kloog et al. 2014).

Statistical analysis

We first assessed the relationship between greenness and continuous birthweight. We constructed a nonlinear model with a natural spline for NDVI and additionally adjusted for all covariates. To test whether the nonlinear model provided a better fit, we used the likelihood-ratio test and compared it to a simpler model with a linear term for NDVI instead. Next, we considered possible effect modification by adding interactions between NDVI and each of newborn sex, maternal education, government support for prenatal care, Census median household income, and Census percent black population. If we found evidence of effect modification by these covariates, they were included in the final model. For greenness and continuous birthweight, the non-linear model without interactions was the final model. The number of degrees of freedom in the natural spline was 4 as increasing this number did not improve model fit. From the final model, we estimated the change to birthweight per IQR increase in NDVI.

We followed a similar process in modeling LBW and SGA, which are binary outcomes. We built a logistic model estimating average changes to the log odds of LBW associated with increased greenness. Although we did not find that the nonlinear model provided a better fit, there was evidence of effect modification by maternal education and newborn sex. For SGA, we also did not find support for a nonlinear model. There was evidence of effect modification by maternal education, government support for prenatal care, and Census median household income. For each of these models, we calculated the odds ratios of the binary outcome per IQR increase in NDVI in each of the population subgroups that demonstrated effect modification via exponentiation of the relevant regression coefficients.

We conducted our analyses using the statistical language R (R Core Team 2017). Statistical significance was set at the 0.05 alpha level. We conducted a sensitivity analysis by using Census tract instead of Census block group as the geography for covariates Census black population proportion and median household income.

Results

Summary Statistics

Table 3-1 shows descriptive statistics of the entire study population and by quartiles of greenness exposure measured with NDVI (1st quartile: < 0.38, 2nd: 0.38 to 0.49, 3rd: 0.49 to 0.60, 4th > 0.60). Birthweight, maternal age, Census median household income, being a first-born, having a married mother, having a white mother, receiving adequate prenatal care, chronic and gestational diabetes, and having a mother with higher education increased while $PM_{2.5}$ exposure, Census black population proportion, receiving government support for prenatal care, and having a mother who had diabetes decreased with increasing greenness quartile.

Table 3-1. Characteristics of Massachusetts full-term, singleton live births by Quartiles of Residential Greenness measured via Normalized Difference Vegetation Index (NDVI) within 250 m buffers from 2001 to 2013

		NDVI Quartile (Range)			
Variable	**Overall**	**1 (< 0.38)**	**2 (0.38 - 0.49)**	**3 (0.49 - 0.60)**	**4 (> 0.60)**
Number of Births (n)	780435	195132	195066	195166	195071
Greenness (NDVI) (mean ± sd)	0.49 ± 0.15	0.29 ± 0.07	0.44 ± 0.03	0.55 ± 0.03	0.67 ± 0.05
Birthweight (g) (mean ± sd)	3441 ± 472	3400 ± 472	3431 ± 472	3456 ± 470	3477 ± 468
$PM_{2.5}$ (µg/m^3) (mean ± sd)	10.1 ± 1.4	10.5 ± 1.4	10.2 ± 1.5	10.0 ± 1.4	9.8 ± 1.3
Clinical Gestational Age (weeks) (mean ± sd)	39.34 ± 1.15	39.37 ± 1.16	39.34 ± 1.15	39.33 ± 1.15	39.33 ± 1.14
Mother's Age (years) (mean ± sd)	30.1 ± 6.0	28.8 ± 6.2	29.8 ± 6.0	30.6 ± 5.8	31.3 ± 5.7
Black Population Proportion in Census Block Group (mean ± sd)	0.08 ± 0.15	0.11 ± 0.17	0.1 ± 0.17	0.07 ± 0.14	0.04 ± 0.10
Median Household Income in Census Block Group ($10,000s) (mean ± sd)	6.77 ± 3.27	5.16 ± 2.70	6.37 ± 3.03	7.31 ± 3.21	8.22 ± 3.31
Black Population Proportion in Census Tract (mean ± sd)	0.08 ± 0.14	0.11 ± 0.15	0.1 ± 0.16	0.07 ± 0.13	0.04 ± 0.09
Median Household Income in Census Tract ($10,000s) (mean ± sd)	6.65 ± 2.82	5.12 ± 2.32	6.3 ± 2.59	7.19 ± 2.71	8.01 ± 2.78
Newborn Female Sex (%)	49.04	49.09	48.89	49.13	49.05
Low Birthweight (%)	2.12	2.49	2.27	1.95	1.77
Small for Gestational Age (%)	9.12	10.15	9.37	8.69	8.29
Parity: first-born (%)	54.74	51.96	53.65	55.58	57.77
Mother Married (%)	68.87	57.07	66.51	73.20	78.70
Government Support for Prenatal Care (%)	33.00	47.59	35.38	27.58	21.45
Smoking Prior to or during Pregnancy (%)	13.71	13.88	13.90	13.84	13.22
Gestational Diabetes (%)	4.04	4.35	4.06	3.93	3.81
Other Diabetes (%)	0.86	0.94	0.93	0.80	0.77
High Blood Pressure during Pregnancy (%)	3.27	3.16	3.26	3.36	3.30
Chronic High Blood Pressure (%)	1.16	1.17	1.21	1.16	1.11

Table 3-1 (Continued)

Season of Birth (%)					
winter	24.41	19.55	22.77	27.19	28.15
spring	25.12	33.74	28.21	24.38	14.13
summer	25.99	32.65	29.66	25.56	16.07
fall	24.48	14.05	19.35	22.88	41.65
Mode of Delivery (%)					
vaginal	65.51	67.37	65.65	64.66	64.38
forceps	0.60	0.57	0.60	0.63	0.61
vacuum	3.57	3.51	3.66	3.61	3.48
first caesarian birth	16.69	16.47	16.94	16.96	16.39
repeat caesarian	12.08	10.65	11.62	12.55	13.48
vaginal birth after previous caesarean birth	1.55	1.43	1.53	1.59	1.65
Maternal Race (%)					
White	71.86	56.11	67.98	77.96	85.38
Black	8.43	11.65	10.18	7.35	4.54
Asian	7.64	9.12	8.55	7.05	5.82
American Indian	0.23	0.21	0.22	0.23	0.25
Other	11.85	22.91	13.07	7.41	4.02
Kessner Index for Prenatal Care (%)					
adequate	78.59	74.55	77.90	80.03	81.91
intermediate	16.95	19.83	17.45	15.95	14.58
inadequate	3.30	4.20	3.48	2.98	2.53
no prenatal care	1.15	1.41	1.17	1.04	0.98
Maternal Education (%)					
Less than High School	10.74	18.37	11.36	7.86	5.37
High School	24.01	30.08	25.30	21.64	19.01
Some College	22.30	20.42	22.45	23.26	23.08
College	26.25	18.54	24.85	29.02	32.58
Advanced Degree	16.70	12.58	16.05	18.23	19.96

Abbreviations: normalized difference vegetation index (NDVI), particulate matter under 2.5 µm in aerodynamic diameter ($PM_{2.5}$), standard deviation (sd)

Continuous Birthweight

The nonlinear model with a natural spline for NDVI was more appropriate for describing the association between greenness and continuous birthweight than the model with a linear term for NDVI ($p < 0.05$). We did not find evidence to support effect modification by newborn sex, maternal education, government support for prenatal care, Census black population proportion, and Census median household income. The nonlinear model with a natural spline and without interactions was thus the final model, whose estimates of the association between greenness and birthweight along the NDVI range are summarized in Table 3-2 and illustrated in Figure 3-1. Overall, the association between greenness and birthweight is positive. Due to sparse data, there was much lower confidence in the estimates for NDVI values below 0.25 and above 0.75. Between NDVI values between 0.25 and 0.75, there was a steep increase in birthweight between 0.25 and 0.50 before flattening out between 0.50 and 0.75. Specifically, the estimated change in birthweight per IQR increase in NDVI (0.22) was 15.88 (95% CI: 12.53, 19.23) g between 0.25 and 0.50 and 7.95 (3.30, 12.60) g.

Table 3-2. Associations between Residential Greenness and Continuous Birthweight in Massachusetts full-term, live singleton births from 2001 to 2013 (n = 780,435)

NDVI Range	**Birthweight Change per IQR increase (0.22) in NDVI (Estimate and 95% CI)**
0 to 0.25	0.02 (-12.35, 12.38)
0.25 to 0.50	15.88 (12.53, 19.23)
0.50 to 0.75	7.95 (3.30, 12.60)
> 0.75	18.84 (-5.46, 43.14)

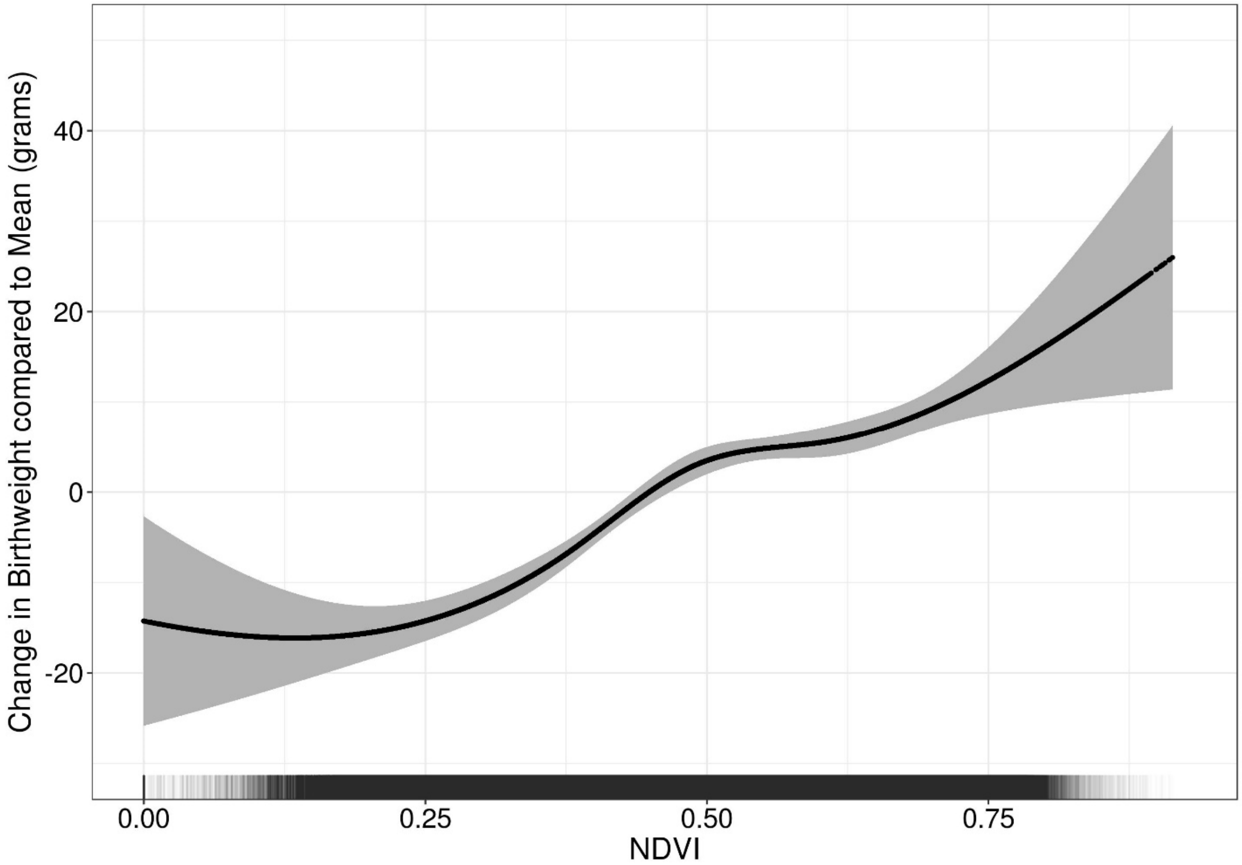

Figure 3-1. Nonlinearity in the Association between Greenness and Birthweight. Black line shows the predicted difference from birthweight at mean NDVI (3,441 grams) in a range of NDVI values, given that all other covariates are at their respective means. 95% confidence intervals are shaded in gray. Rug plots on x-axes represent density of observed greenness exposures.

Low Birthweight

The logistic model with a natural spline for NDVI, describing the association between greenness and odds of LBW, did not provide improvement over the logistic model with a linear term for NDVI. However, there was strong evidence suggesting that the association between greenness and birthweight was modified by maternal education. A logistic model with all main effects plus interactions between NDVI and maternal education was the most appropriate of the models tested ($p < 0.05$). With increased greenness, the odds for LBW decreased for those born to mothers with a high school or college education (Figure 3-2). The point estimates for decreased odds of LBW with increased greenness was most negative for those born to mothers with a college education followed, in order, by high school, advanced degree, some college, and less than high school. Estimates and 95% CIs are summarized in Table 3-3.

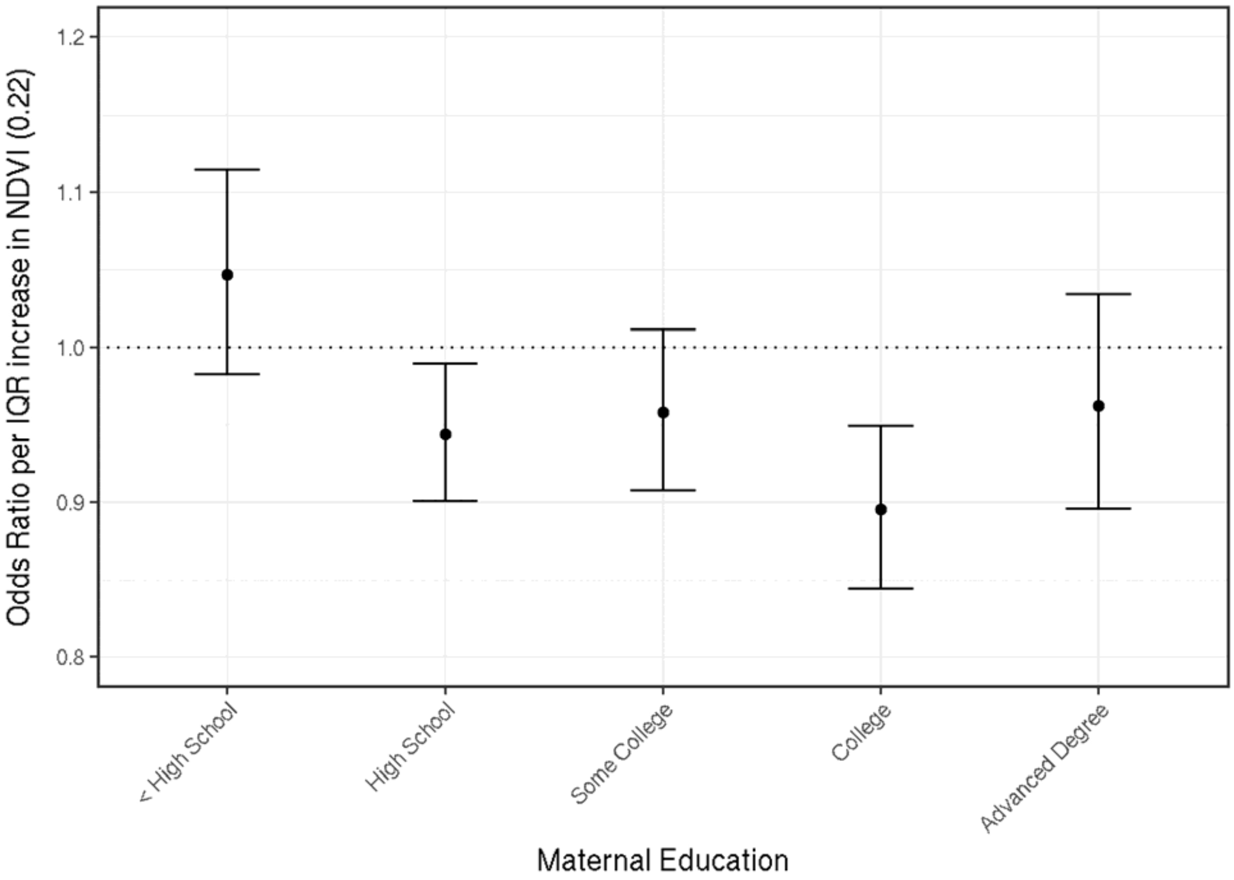

Figure 3-2. Effect Modification by Maternal Education in the Association between Greenness and Low Birthweight (LBW). Odds ratios and 95% confidence intervals for LBW per IQR increase in NDVI (0.22) are shown. Dotted line at 1.0 represents a null association.

Table 3-3. Associations between Residential Greenness and Odds of Low Birthweight (LBW) and Small for Gestational Age (SGA) in Massachusetts full-term, live singleton births from 2001 to 2013 (n = 780,435). The odds ratio and 95% confidence interval per IQR increase in NDVI are shown for each subgroup. For LBW, maternal education and newborn sex were effect modifiers. For SGA, maternal education, government support for prenatal care, and Census median household income were effect modifiers.

		Odds Ratio per IQR increase (0.22) in NDVI (Estimate and 95% CI)
Low Birthweight		
Maternal Education (Highest Level Attained)		
	< High School	1.05 (0.98, 1.11)
	High School	0.94 (0.90, 0.99)
	Some College	0.96 (0.91, 1.01)
	College	0.90 (0.84, 0.95)
	Advanced Degree	0.96 (0.90, 1.03)
Small for Gestational Age		
Maternal Education (Highest Level Attained)		
	< High School	1.00 (0.96, 1.03)
	High School	0.94 (0.91, 0.96)
	Some College	0.95 (0.92, 0.97)
	College	0.94 (0.91, 0.96)
	Advanced Degree	0.97 (0.94, 1.00)
Government Support for Prenatal Care		
	No	0.94 (0.92, 0.95)
	Yes	0.97 (0.95, 0.99)
Census Median Household Income		
	< 40,000	0.95 (0.93, 0.98)
	40,000 - 56,500	0.97 (0.94, 1.00)
	56,500 - 72,000	0.97 (0.94, 1.00)
	72,000 - 92,500	0.94 (0.91, 0.97)
	> 92,500	0.94 (0.91, 0.97)

Small for Gestational Age

Similar to the LBW models, the nonlinear logistic model for SGA did not improve upon the logistic model with a linear term for greenness. The association between greenness and odds for SGA was modified by maternal education (Figure 3-3), government assistance for prenatal care (Figure 3-4), and Census median household income (Figure 3-5). A logistic model with all main effects and interactions with these effect modifiers was the most appropriate ($p < 0.05$). Overall, with increased greenness, the odds of SGA decreased. However, the decrease was larger for those born to mothers who attained at most a high school, some college, or college education compared to those born to mothers who did not attain a high school education or completed an advanced degree. The decrease in odds for those without government assistance for prenatal care was larger in magnitude compared to those with government assistance. Finally, we divided the sample population into quintiles of Census median household income quintiles and estimated the associations between greenness and odds of SGA in each of the quintiles. The decrease was largest for those in \$72,000 – \$92,500 income quintile, followed by > \$92,500, < \$40,000, \$40,000 – \$56,500, and \$56,500 – \$72,000. Estimates and 95% CIs are found in Table 3-3.

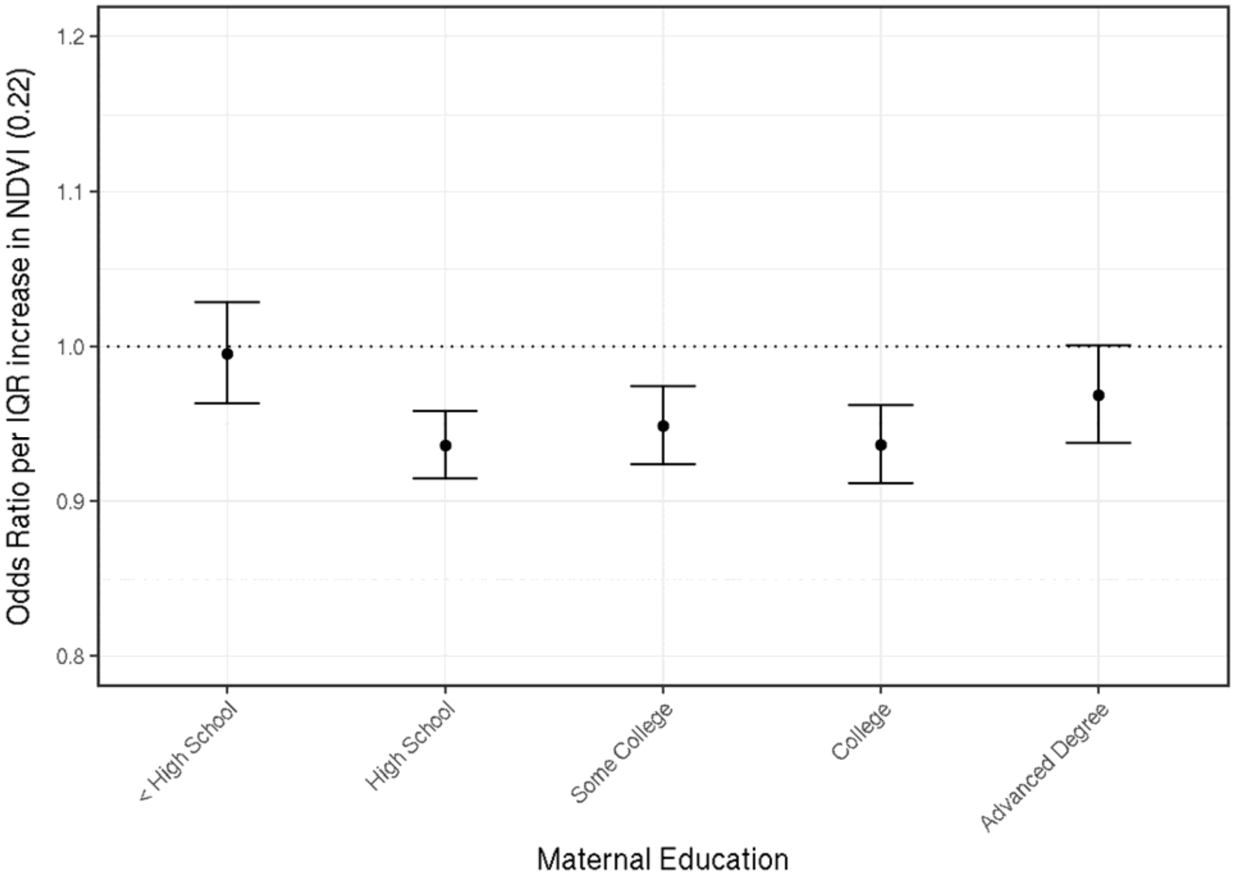

Figure 3-3. Effect Modification by Maternal Education in the Association between Greenness and Small for Gestational Age (SGA). Odds ratios and 95% confidence intervals for SGA per IQR increase in NDVI (0.22) are shown. Dotted line at 1.0 represents a null association.

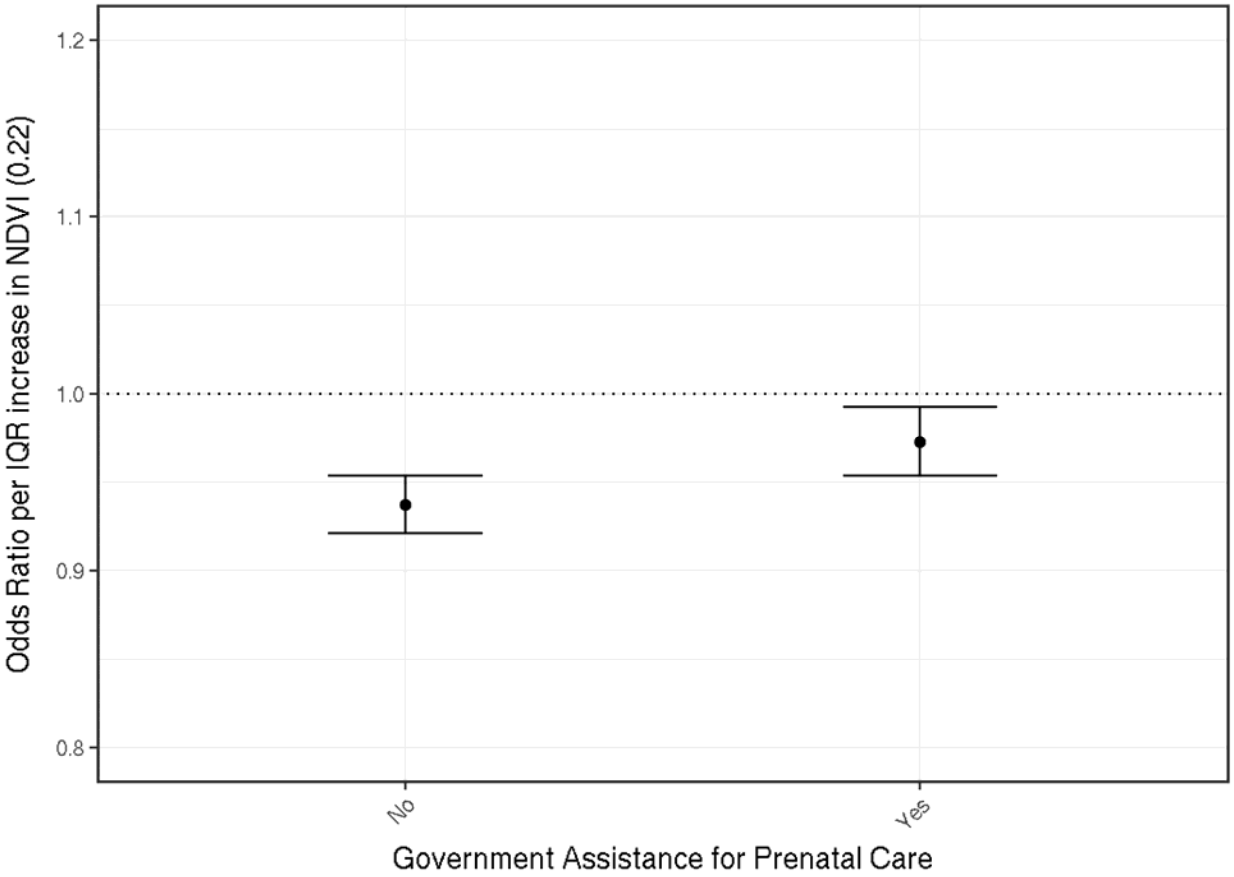

Figure 3-4. Effect Modification by Government Support for Prenatal Care in the Association between Greenness and Small for Gestational Age (SGA). Odds ratios and 95% confidence intervals for SGA per IQR increase in NDVI (0.22) are shown. Dotted line at 1.0 represents a null association.

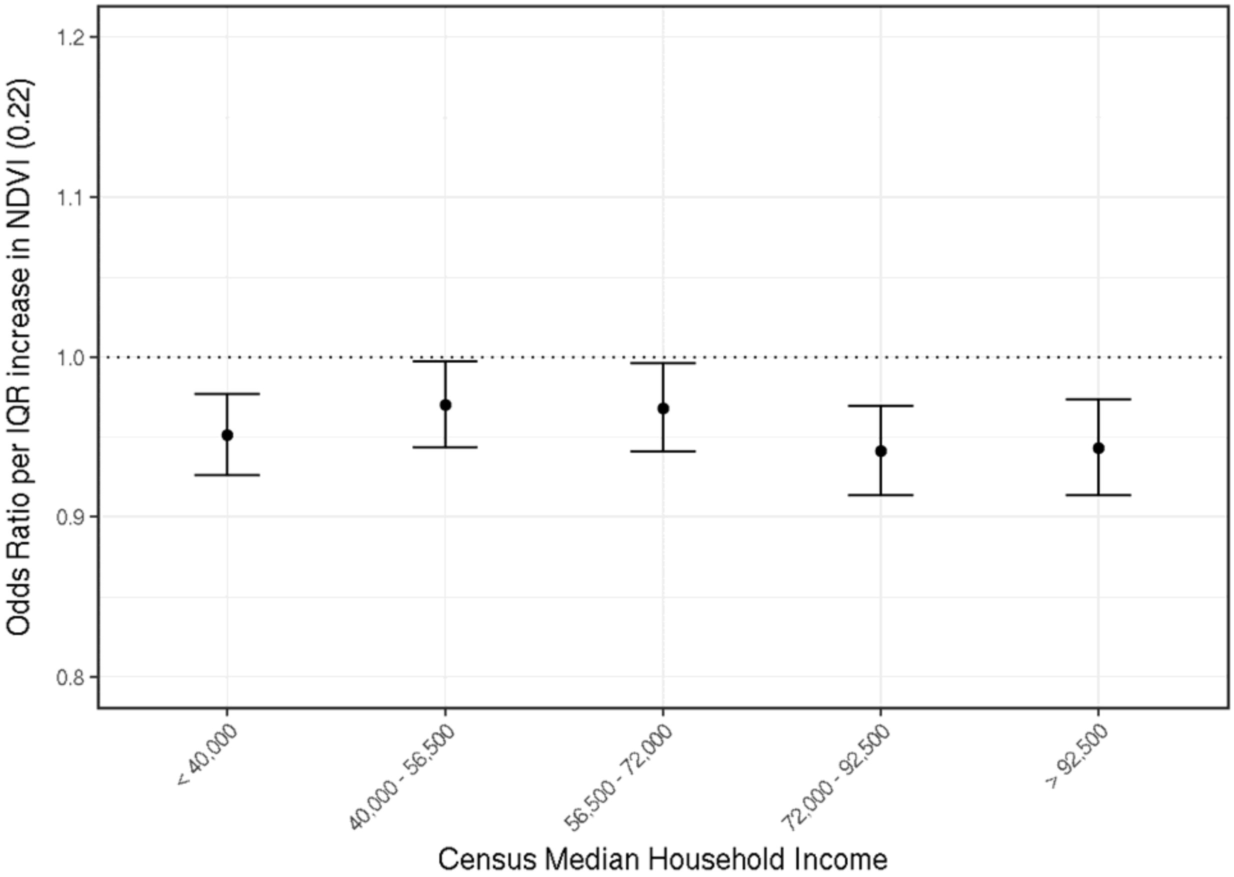

Figure 3-5. Effect Modification by Census Median Household Income in the Association between Greenness and Small for Gestational Age (SGA). Odds ratios and 95% confidence intervals for SGA per IQR increase in NDVI (0.22) are shown. Dotted line at 1.0 represents a null association.

Discussion

In our analysis of Massachusetts births from 2001 to 2013, the association between maternal exposure to residential greenness during pregnancy and newborn birthweight was positive overall. The majority of the previous literature also found a positive relationship between greenness and birthweight, and the estimates from our analysis fall in the range of existing estimates (Banay et al. 2017). Large positive associations were found in British Columbia, where a 0.1 NDVI increase was associated with a 20.6 (95% CI: 16.5, 24.7) g increase in birthweight (Hystad et al. 2014); in a study in Tel Aviv, Israel, where a 0.06 NDVI increase was associated with a 19.2 (95% CI: 13.3, 25.1) g increase in birthweight (Agay-Shay et al. 2014); and in a pooled analysis of 4 Spanish birth cohorts a 38.3 (95% CI: 17.1, 59.5) g per 0.19 NDVI increase) (Dadvand et al. 2012). Several mechanisms could explain the association between greenness and higher birthweights. The main pathways are mitigating harmful environmental exposures, restoring mental capacity, and providing a setting for social interactions as well as physical activity (Frumkin et al. 2017; James et al. 2015; Markevych et al. 2017). Vegetation such as trees, through photosynthesis, filter the air and serve as physical barriers to heat, air, and noise pollution (Banay et al. 2017; James et al. 2015). Traffic air pollution has been shown to be considerably lower in areas of high greenness (Dadvand et al. 2015). Multiple studies have found that cognitive function and mental capacity improve with increased greenness exposure (Frumkin et al. 2017; Markevych et al. 2017). Moreover, since greenness often occurs in recreational spaces such as parks, high greenness is often indicative of proximity to places where people can meet socially or exercise, improving health through social cohesion and physical activity. Finally, although research directly looking at physiological responses to greenness is scarce, experiments have shown that proximity to greenness is associated with greater autonomic activity via measurements of heart rate variability (Choi et al. 2016). Other physiological findings include less pronounced response to stress and better immune function (Wilker et al. 2014). Greenness can impact maternal health during pregnancy through a combination of the proposed mechanisms and affect the fetal environment leading to changes in birthweight. Since there exist several mechanisms through which greenness can affect health, nonlinearity in and effect modification of the associations between greenness and birthweight are also expected.

We found a nonlinear relationship between greenness and continuous birthweight (Figure 1). Between low to medium levels of greenness, or 0.25 to 0.50 NDVI, the association was strongly positive. Between medium to high levels of greenness, 0.50 to 0.75 NDVI, the association was positive but much lower in magnitude. The characterization of a nonlinear dose-response relationship between greenness and birthweight has not been previously reported unlike nonlinearity for other outcomes such as physical activity (James et al. 2017). In some prior studies of greenness and birthweight, it was not possible to determine the shape of the dose-response relationship since greenness exposure was classified into quantiles of NDVI (Banay et al. 2017; Cusack et al. 2017a) Some studies considered NDVI on the continuous scale and one prior study used quadratic and cubic splines in their analysis but did not find a departure from linearity (Casey et al. 2016). It is possible that the pathways through which greenness impacts health are present at medium levels of greenness and going beyond this threshold do not advance the impacts further. This may explain the why positive, null, or even negative associations were found in existing literature (Banay et al. 2017). A recent study of over 3 million birth records in Texas found only a 1.9 (95% CI: 0.1, 3.7) g increase in birthweight when comparing those in the highest quartile of greenness (NDVI > 0.52) versus those in the lowest quartile (NDVI < 0.37)

(Cusack et al. 2017a). Another study by Cusack et al. found a positive association for those born in Portland, Oregon but a negative association for those born in Austin, Texas (Cusack et al. 2017b). Some studies did not find significant changes in birthweight with increased greenness or proximity to green spaces (Abelt and McLafferty 2017; Grazuleviciene et al. 2015). Importantly, nonlinearity between greenness and health has policy implications. When considering potential benefits to birthweight by increasing greenness, it may be more beneficial to focus on developing areas from low greenness to medium greenness as opposed to developing from medium greenness to high greenness. However, as this is a novel finding, further investigation of the dose-response relationship between greenness and birthweight is needed.

For associations between greenness and binary outcomes LBW and SGA, we found evidence of effect modification by SES. With LBW, it was modified by maternal education; with SGA, it was modified by maternal education, government assistance to prenatal care, and Census median household income. The inconsistency in the set of effect modifiers was expected since LBW and SGA are defined differently, with SGA taking gestational age into account while LBW setting a cutoff at 2,500 g. Overall, the strongest negative associations were found for those in higher SES groups, indicated by being born to a mother in higher education groups, not having government assistance for prenatal care, and living in areas with higher median household income (Figures 3-2, Figure 3-3, Figure 3-4, Figure 3-5). This contrasts existing studies that showed stronger associations among those born to mothers with lower levels of education (Agay-Shay et al. 2014; Dadvand et al. 2012; Markevych et al. 2014), or those that did not find evidence of effect medication by SES (Casey et al. 2016; Ebisu et al. 2016). As there are few existing studies that investigated effect modification in greenness and LBW or SGA, consensus understanding of how SES interacts with greenness is still unclear (Banay et al. 2017).

Our study had several strengths. With a final sample size of 780,435, our study represents the second largest analysis of birthweight to date (Banay et al. 2017; Cusack et al. 2017a). Thus, we had high statistical power and the ability to assess nonlinear associations. Moreover, our analyses adjusted for air pollution, which few past studies have done (Agay-Shay et al. 2014; Cusack et al. 2017a). Greenness has previously been shown to be protective of the detrimental health effects from air pollution and therefore, adjustment for it is important since greenness may act through different pathways to those of air pollution in how it impacts maternal health and consequently, fetal growth during pregnancy (James et al. 2015; Nowak et al. 2006). Finally, in contrast to prior studies that determined greenness exposure using a single satellite image from a single summer day (Abelt and McLafferty 2017; Ebisu et al. 2016; Grazuleviciene et al. 2015), our choice to use multiple measurements of NDVI to calculate greenness exposure during pregnancy captured the time-varying nature of greenness, which peaks in summer and is at its lowest during winter. This likely led to a more accurate depiction of maternal greenness exposure and reduced misclassification.

Our analyses had limitations. Using the maternal residence reported at the time of birth as the basis for calculating greenness exposure could have led to exposure misclassification. Not only could the residence change or be reported incorrectly, our conclusions are limited specifically to the relationship between residential greenness and birthweight. Even when the reported residence was accurate, maternal exposure to greenness was unlikely to pertain only to the area around the maternal residence, but also to areas of employment. It was probable, since most people commute to more urban areas for work and that these urban areas are often lower in greenness than residential areas, for the comprehensive exposure to greenness to be lower than the residential greenness. On average, across all mothers, residential greenness was likely higher than comprehensive greenness, which would have led to estimated associations between greenness and birthweight that were biased toward the null. Unfortunately, we did not have detailed information on whether a mother moved nor their location history during pregnancy. Furthermore, using NDVI to ascertain greenness did not inform on specific types of vegetation such as trees, grass, shrubs. How people interact with greenness depending on the type of vegetation can be very different and without this information, we are unable to devise detailed policy implications (Banay et al. 2017; James et al. 2015). The variety of associations in the existing literature could be due to differences in vegetation across the study settings. Finally, by using 250 * 250 m as the spatial resolution, we assumed that pathways through which greenness influence health were limited to the local residential area. While prior studies found no considerable differences in associations when using 100, 250, 500, and 1250 m spatial resolutions (Abelt and McLafferty 2017; Agay-Shay et al. 2014; Casey et al. 2016), we limited the generalizability of our results to local residential greenness by using the 250 m spatial resolution. Our analysis included many covariates to minimize confounding but, as with many studies, there remained unmeasured and residual confounding. We assessed the strength of confounding by each covariate and found that clinical gestational age, season of birth, maternal smoking, maternal education, particulate air pollution, parity, and maternal race were the strongest confounders (Figure 3-1). Finally, missingness and measurement error in the birth records could have led to biases in either direction. Missingness was assumed to be random; we did not find an association between missingness with either greenness or birthweight for those missing covariate data. Exclusions due to missing covariate data were relatively few at less than 6% of the final sample size. It was not possible to ascertain the level of measurement error in the exposure without another set of concurrent NDVI measurements during the study period. With the outcome, birthweight, we believe it was accurately measured given the ubiquity of the measurement. Any biases from outcome measurement error was most likely non-differential.

Maternal exposure to residential greenness during pregnancy was associated with increased birthweight as well as lower odds of LBW or SGA. The relationship between greenness and continuous birthweight was nonlinear with larger increases from low to medium NDVI than from medium to high NDVI. The association between greenness and LBW and SGA was modified by SES, with more negative associations in higher SES groups. While the overall relationship between greenness and increased birthweight was consistent with existing literature, our finding of a nonlinear relationship is novel and effect modification results contrast conclusions from prior studies. Therefore, further research into these topics, along with how different types of vegetation influence birthweight is warranted. Answering these questions will help guide policy to maximize health of the population.

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Study 4. Estimating the Effects of Neighborhood Social Stress and Privilege on Birthweight: Applying the Index of Concentration of Extremes (ICE) and Examining Effect Modification by Indicators of Individual Socioeconomic Status

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Abstract

Background: Neighborhood measures of socioeconomic status (SES) are important determinants of health. We therefore investigate the association between the Index of Concentration at the Extremes (ICE), a measure of neighborhood SES, and birthweight, an important newborn health outcome.

Methods: We considered two established ICE measures, one based on race, and another on income to build multivariate regression models to estimate associations with continuous birthweight. We assigned ICE measures to each birth based on the Census block group that the mother resided in during pregnancy. Our study population was restricted to singleton full-term live births born to black and white mothers in Massachusetts from 2001 to 2013 (n = 629,675).

Results: Increased neighborhood SES was associated with higher birthweight and this association was modified by maternal race and Medicaid status. Higher ICE measures was associated with higher birthweights. With the ICE based on race, the association was stronger among those born to white mothers and among those without Medicaid. With the ICE based on income, the association was stronger among those born to white mothers and among those with Medicaid. These patterns in associations were robust to expanding the geographic definition of a neighborhood to Census block group and to including a random intercept for neighborhood.

Conclusions: In a large birth cohort, neighborhood SES, as measured by ICE, was associated with higher birthweight. Maternal race and Medicaid status modified the association with most evidence suggesting stronger associations among those with higher individual SES.

Introduction

Neighborhood socioeconomic status (SES) is a major determinant of health. People, especially vulnerable populations such as children and the elderly, who reside in areas with lower SES often have worse health outcomes (Diez Roux 2001; Shmool et al. 2015, 2014). Uneven development of infrastructure results in unequal access to health services, nutrition, education, housing, and more (Morello-Frosch and Lopez 2006; Shmool et al. 2014). Differences in neighborhood SES can also impact social cohesion and interactions, leading to psychosocial health consequences (Diez Roux 2001). Thus, there exists a need to quantify neighborhood SES and understand their potential health implications.

The index of concentration of extremes (ICE) is an attempt to measure neighborhood SES (Feldman et al. 2015; Huynh et al. 2017; Krieger et al. 2017b; Massey 2001). An ICE describes, simultaneously, the geographic concentration of two groups, often chosen to be two that are at opposite extremes of SES. It therefore contrasts an inequality index such as the Gini, on which an area with high SES and an area with low SES can have the same value (Huynh et al. 2017). There are other indices that are similarly directional in neighborhood SES like the ICE but are based on a combination of SES indicators (Kane et al. 2017). An index based on multiple factors can be disadvantageous for making explicit interpretations or policy recommendations since changes in such an index can stem from a choice or combination of multiple factors (Feldman et al. 2015). An ICE measure avoids this because it restricts itself to describe the geographic concentration of two groups related by one or the same set of characteristics. In prior studies using ICE measures and health outcomes, researchers calculated and used as an exposure the ICE based on race or income (Feldman et al. 2015; Huynh et al. 2017; Krieger et al. 2017b).

We therefore investigate the associations between ICE measures and birthweight, a ubiquitous newborn health outcome. Decreased birthweight is a risk factor for chronic diseases and premature mortality (Barker et al. 1993; Belbasis et al. 2016; Boulet et al. 2011; Hack et al. 1995; Reyes and Mañalich 2005). Low neighborhood SES has been shown to be associated with poor birth outcomes such as decreased birthweight (Ncube et al. 2016; Subramanian et al. 2006). However, published research on SES and birthweight has focused on individual characteristics (Ncube et al. 2016; Subramanian et al. 2006). In a time when health disparities and geographic segregation in SES has grown, there is a need to ascertain the health consequences of geographic polarization of SES (Dwyer 2010; Krieger et al. 2017b). We hypothesize those born to mothers who resided in neighborhoods of high privilege during pregnancy, as indicated by ICE measures, have higher birthweights. We also allow for differences in associations depending on maternal race and individual SES, which have been shown to be sources of effect modification in the relationship between neighborhood SES and birth outcomes (Ncube et al. 2016; Rauh et al. 2001).

Methods

Indices of Concentrations of Extremes

Using five-year estimates of Census data from the 2010 American Community Survey, we calculated the index of concentrations of extremes (ICE) for race and income in each Census block group in Massachusetts. The general calculation for ICE is as follows (Krieger et al. 2017b; Massey 1996):

$$ICEi = (Ai - Pi) / Ti \tag{4.1}$$

Where Ai represents the number of the most privileged, Pi the number of least privileged, and Ti the total number with observed data in neighborhood i. For the ICE based on race, ICE_{race}, the most privileged group was the number of persons who reported to be white and the least privileged was those who reported to be black in a Census block group, which we considered to be a neighborhood. For the ICE based on income, ICE_{income}, the most privileged group were the number of households earning equal or more than $100,000 per year and the least privileged were those earning less than $25,000 per year. These two cut points correspond to the 70th and 20th percentiles of annual household income in Massachusetts in 2010 respectively (U.S. Census Bureau 2017). ICE_{race} and ICE_{income} each ranged from -1 (least privileged) to 1 (most privileged). In other words, for a given neighborhood, -1 means that 100% of the population or households is concentrated into the least privileged group while 1 means that 100% of the population or households is concentrated into most privileged group.

Study population

Our study base started with all birth records between January 1, 2001 and December 31, 2013 in Massachusetts (n = 978,225). We excluded those with missing address information (n = 23,943), those with a birthweight below 500 g (n = 772), and those that were not live births (n = 8,621), nor singletons (n = 42,186), nor full-term (n = 77,036). Full-term births were those with a recorded gestational age between 37 and 44 weeks, determined through ultrasound or physical examination by a clinician at the latest prenatal visit or at birth. As ICE_{race} describes the polarization of white and black subpopulations, we restrict our analysis to those born to white and black mothers, which excluded a further 154,296 births or 19% of the total number of births during the study period. In addition to birthweight, the birth records included information about the pregnancy itself, such as gestational age, as well as maternal characteristics, such as race and highest educational level attained, which were used in statistical analysis. After excluding those with missing covariate data (n = 41,696), the final sample size was 629,675. Each maternal residential address was geocoded by the Massachusetts Department of Public Health against TomTom Multinet using AccuMail address and zip code as the input address field and zone. These geocodes allowed us to link each birth to its Census block group and associated ICE measures. The use of these data was approved by the Massachusetts Department of Public Health and the human subjects committee at the Harvard T. H. Chan School of Public Health.

Statistical Analysis

The outcome of our regression models was continuous birthweight in grams. We started by building univariate regression models for ICE_{race} and ICE_{income}. We then built multivariate models adjusted for covariates selected a priori based on those used in prior studies (Gray et al. 2014; Shmool et al. 2015; Subramanian et al. 2006). They include maternal age (years), maternal race (white, black), maternal marital status (married, not married), maternal smoking prior to or during pregnancy (yes, no), maternal education (highest level of education attained: less than high school, high school, some college, college, advanced degree beyond college), parity (first-born, not first-born), maternal diabetes (yes, no), gestational diabetes (yes, no), maternal chronic high blood pressure (yes, no), maternal high blood pressure during pregnancy (yes, no), Kessner index of adequacy of prenatal care (adequate, intermediate, inadequate, no prenatal care) (Kessner et al. 1973), birth mode of delivery (vaginal, forceps, vacuum, first caesarian birth, repeat caesarian birth, vaginal birth after caesarian birth), clinical gestational age (weeks), year of birth (one of 2001 to 2013), newborn sex (male, female), and Medicaid status (yes, no). In addition, we included particulate air pollution under 2.5 μm in diameter ($PM_{2.5}$) since maternal exposure to $PM_{2.5}$ during pregnancy is negatively associated with birthweight (Bell et al. 2010; Dadvand et al. 2013; Darrow et al. 2011; Kloog et al. 2012; Stieb et al. 2012; Sun et al. 2016). Each birth's $PM_{2.5}$ exposure was calculated by calculating the average of daily $PM_{2.5}$ predictions of the 1 * 1 km grid pixel of the maternal residential address during the entire pregnancy. The $PM_{2.5}$ data came from a hybrid prediction model that used remote sensing and land use variables; its out-of-sample R^2 was consistently above 0.8 (Kloog et al. 2014).

We considered possible effect modification by maternal race and individual SES as this has been shown in prior studies (Ncube et al. 2016; Rauh et al. 2001). In our final models, we included an interaction between the ICE measure and each of maternal race and Medicaid status. Maternal race was reported in the birth records along with Medicaid status, which acts as an appropriate indicator of individual SES since its eligibility is based on annual income (US Department of Labor 2018). Those who reported as having Medicaid status had their prenatal care supported by the government.

We conducted sensitivity analyses by substituting the ICE measures based on Census block group with ICE measures based on Census tracts and by including a random intercept for neighborhood in the final models. Census block groups are smaller geographical subdivisions than Census tracts, which gives ICE measures at the Census block group higher variability. Inclusion of a random intercept for neighborhood (Census block group or tract) allowed differences in associations to be explained by unmeasured characteristics within individual neighborhoods. We used R 3.4.1 for data linkage and statistical analyses (R Core Team 2017).

Results

The characteristics of the study population are show in Table 4-1. ICE_{race} had a median value much closer to 1 than ICE_{income}, which reflects that the majority of the population in Massachusetts was white. More than two-thirds of the mothers were married and more than one-third used Medicaid for the newborn's prenatal care. Over 80% of the newborns received adequate prenatal care according to the Kessner index and over 90% of the mothers had at least a high school education.

Table 4-1. Characteristics of the Analysis Set of Massachusetts Births between Years 2001 and 2013 (n = 629,675). Study population was restricted to those born to white and black mothers.

Variable	**Overall**
Total Births (n)	629675
Continuous Variables (median ± IQR)	
Birthweight in Grams	3459 ± 623
Average $PM_{2.5}$ over entire Pregnancy (1 km buffer) ($\mu g/m^3$)	10.2 ± 2.3
Clinical Gestational Age in Weeks	39 ± 1
Mother's Age in Years	31 ± 8.17
ICE for Race	
at Census Block Group	0.88 ± 0.27
at Census Tract	0.86 ± 0.24
ICE for Income	
at Census Block Group	0.12 ± 0.43
at Census Tract	0.12 ± 0.37
Binary and Categorical Variables (%)	
Infant Sex = Female	49.1
Maternal Marital Status = Married	72.0
Medicaid Status	28.2
Smoking During or Prior to Pregnancy	15.2
Gestational Diabetes	3.7
Other Diabetes	0.8
High Blood Pressure during Pregnancy	3.6
Chronic High Blood Pressure	1.3
Parity: First-Born	45.2
Mode of Delivery	
Vaginal	64.9
Forceps	0.6
Vacuum	3.5
First Caesarian Birth	17.1
Repeat Caesarian	12.4
Vaginal Birth after Previous Caesarean Birth	1.5
Maternal Race	
White	89.5
Black	10.5
Kessner index for adequacy of prenatal care	
Adequate	80.3
Intermediate	15.6
Inadequate	3.0
No Prenatal Care	1.2
Maternal Education	
Less than High School	7.4
HS/GED	22.8
Some College	23.7
College	28.5
Advanced Degree	17.6

Racial and economic ICE measures were positively associated with continuous birthweight. In univariate analyses, birthweight was, on average, 33 (95% CI: 32, 34) g higher per IQR increase in ICE_{race} (0.27) and 61 (95% CI: 59, 63) g higher per IQR increase in $\text{ICE}_{\text{income}}$ (0.43). The estimated associations in the fully-adjusted model were attenuated and closer to the null: 10 (95% CI: 8, 10) g higher per IQR increase in ICE_{race} and 15 (95% CI: 13, 16) g higher per IQR increase in $\text{ICE}_{\text{income}}$. Additionally, we found evidence for effect modification by maternal education and Medicaid usage ($p < 0.05$). On average, per IQR increase in ICE_{race}, the associated increase in birthweight was 5 (4, 7) g in those born to black mothers compared to 11 (10, 13) g in those born to white mothers and 6 (5, 8) g among those born to those with Medicaid-supported prenatal care compared to 11 (10, 13) g among those without (Figure 4-1). There were similarly differences in associations per IQR increase in $\text{ICE}_{\text{income}}$: 4 (1, 8) g among those born to black mothers compared to 10 (9, 11) g among those born to white mothers and 28 (25, 31) g among those with Medicaid and 8 (6, 11) g among those without (Figure 4-2).

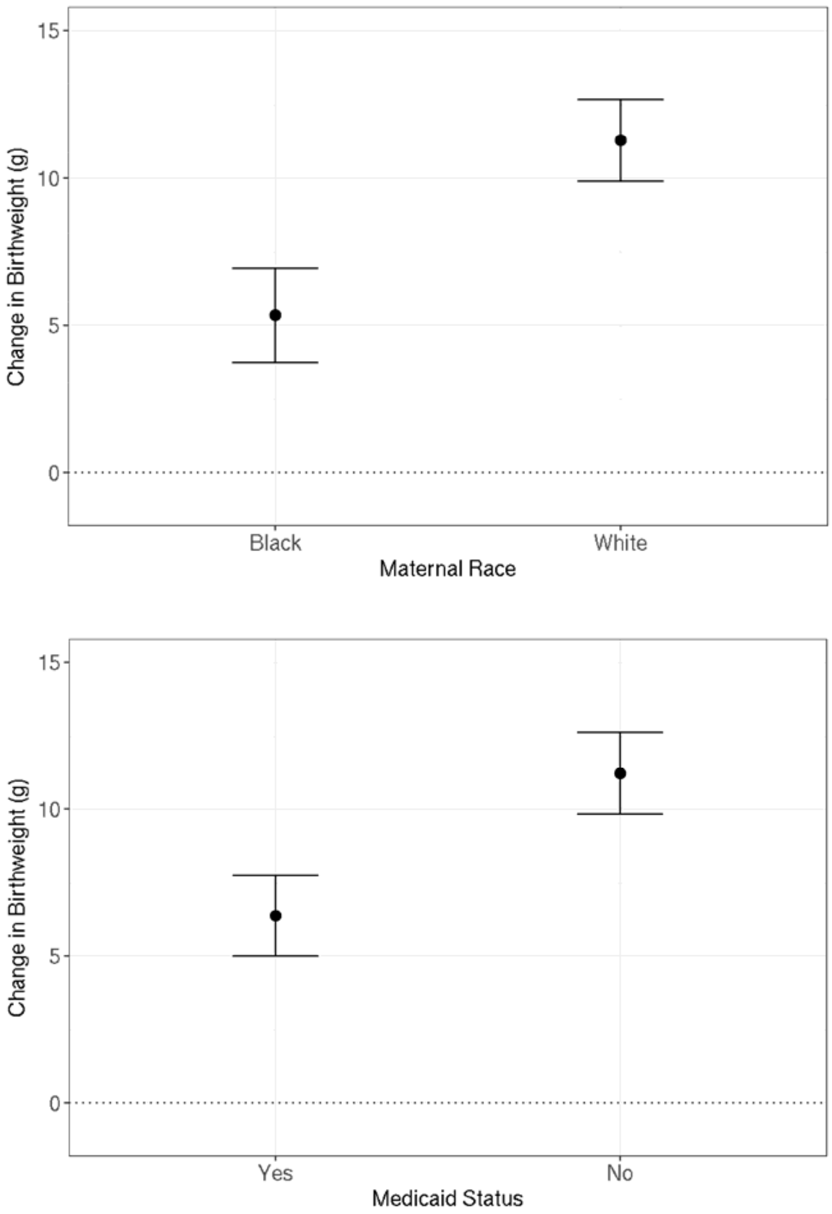

Figure 4-1. Association between an Interquartile Range Increase in ICE_{race} (0.27) and Continuous Birthweight in Massachusetts from 2001 to 2013 (n = 629,675). Average changes in birthweight and 95% confidence intervals are presented separately for those born to black mothers and those born to white mothers (top), and separately for those born to mothers who received Medicaid for prenatal care and those who did not (bottom).

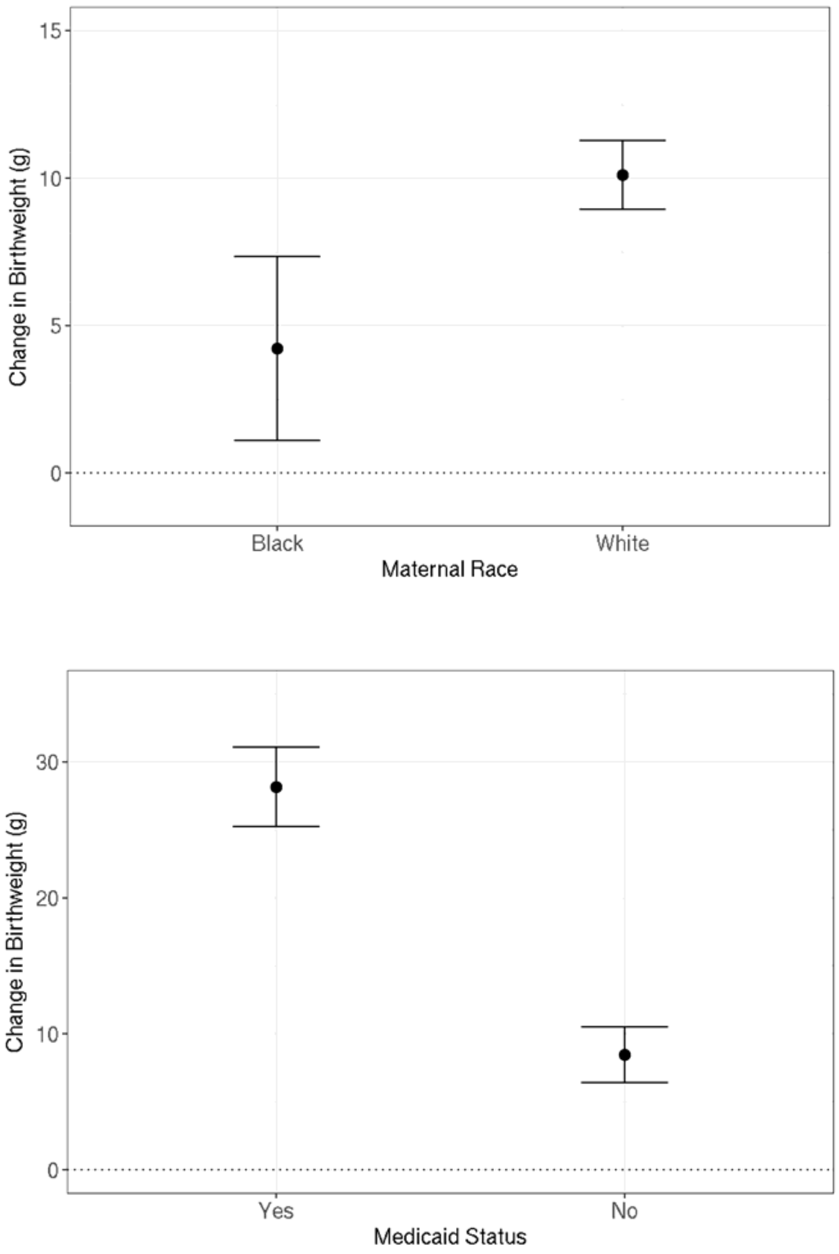

Figure 4-2. Association between an Interquartile Range Increase in $\text{ICE}_{\text{income}}$ (0.43) and Continuous Birthweight in Massachusetts from 2001 to 2013 (n = 629,675). Average changes in birthweight and 95% confidence intervals are presented separately for those born to black mothers and those born to white mothers (top), and separately for those born to mothers who received Medicaid for prenatal care and those who did not (bottom).

Table 4-2. Associations between an Interquartile Range Increases in ICE_{race} (0.27) or $\text{ICE}_{\text{income}}$ (0.43) and Continuous Birthweight in Massachusetts from 2001 to 2013 (n = 629,675).

	Average Change in Birthweight in Grams per Interquartile Increase (95% CI)	
	in ICE_{race}	**in $\text{ICE}_{\text{income}}$**
Main Effects		
Census Block Group		
No Random Intercept		
Overall	8.75 (7.67, 9.82)	14.73 (13.02, 16.45)
Random Intercept for Neighborhood		
Overall	9.65 (8.32, 10.98)	10.19 (8.78, 11.59)
Census Tract		
No Random Intercept		
Overall	9.02 (8.00, 10.04)	18.08 (16.23, 19.82)
Random Intercept for Neighborhood		
Overall	11.82 (10.02, 13.63)	14.31 (12.30, 16.31)
Maternal Race		
Census Block Group		
No Random Intercept		
Black	5.35 (3.75, 6.95)	4.23 (1.1, 7.35)
White	11.29 (9.9, 12.67)	10.11 (8.95, 11.27)
Random Intercept for Neighborhood		
Black	7.05 (5.16, 8.93)	3.18 (-0.27, 6.63)
White	11.6 (9.93, 13.27)	11.08 (9.61, 12.54)
Census Tract		
No Random Intercept		
Black	5.46 (3.98, 6.94)	6.44 (3.22, 9.67)
White	11.98 (10.62, 13.33)	12.36 (11.18, 13.55)
Random Intercept for Neighborhood		
Black	6.88 (5.14, 8.63)	5.07 (1.53, 8.61)
White	11.9 (10.29, 13.52)	13.27 (11.78, 14.76)
Medicaid Status		
Census Block Group		
No Random Intercept		
Yes	6.37 (5, 7.75)	28.17 (25.24, 31.1)
No	11.23 (9.83, 12.63)	8.48 (6.44, 10.52)
Random Intercept for Neighborhood		
Yes	7.71 (6.1, 9.32)	25.43 (22.09, 28.77)
No	11.64 (10.02, 13.27)	11.27 (8.79, 13.76)
Census Tract		
No Random Intercept		
Yes	7.02 (5.71, 8.33)	30.72 (27.83, 33.62)
No	11.11 (9.78, 12.45)	11.81 (9.72, 13.89)
Random Intercept for Neighborhood		
Yes	8.13 (6.6, 9.65)	28.13 (24.82, 31.44)
No	11.18 (9.63, 12.72)	14.48 (11.96, 16.99)

Patterns of associations were robust to defining a neighborhood as a Census tract instead of a Census block group; the estimates were slightly more conservative when Census block group was used (Table 4-2). Moreover, statistical inferences and patterns in effect modification were also robust to adding a random intercept for neighborhood.

Finally, we assessed the relative amount of confounding by each covariate (Figure 4-3 and Figure 4-4). Maternal race was the largest source of confounding in the relationship between ICE measures and continuous birthweight. Other strong confounders include maternal smoking, parity, clinical gestational age, maternal marital status, Medicaid status, maternal education, and $PM_{2.5}$ exposure during pregnancy.

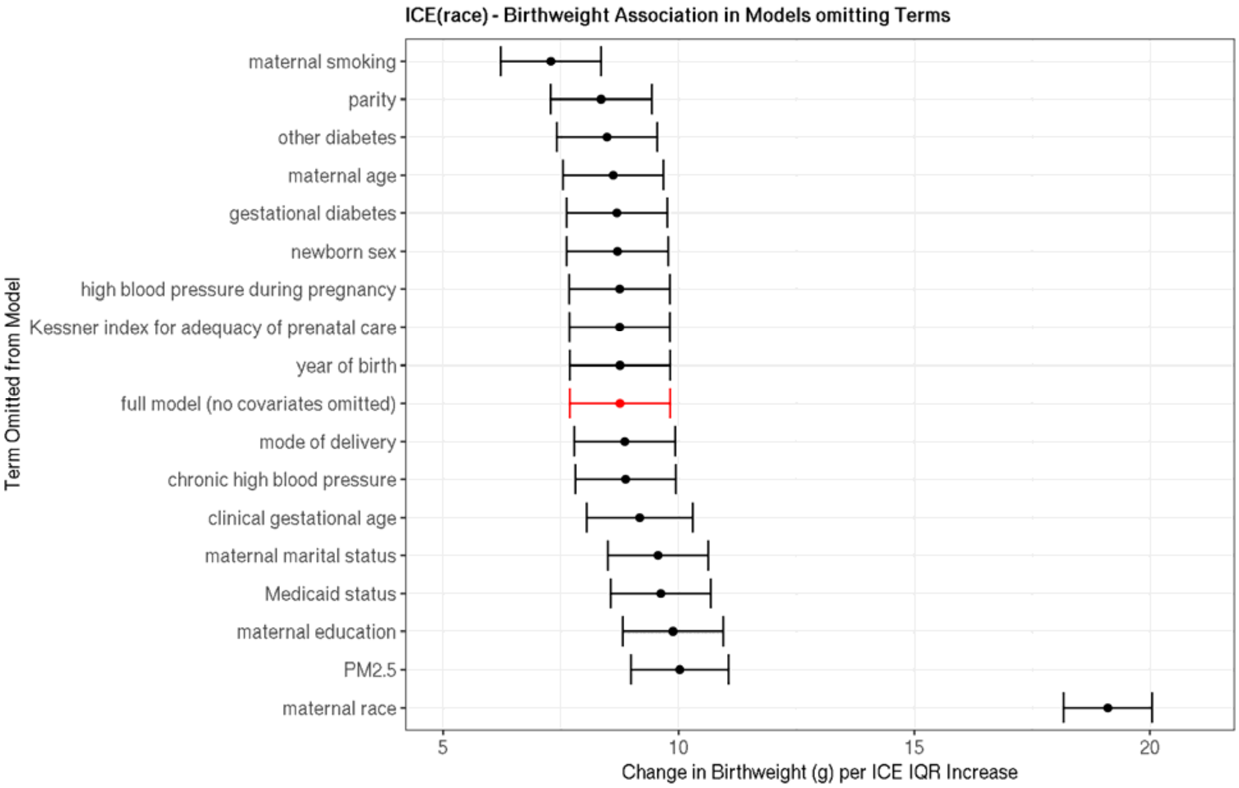

Figure 4-3. Assessment of Confounding by Covariates in the Relationship between Index of Concentration of Extremes (ICE) for Race and Birthweight in Massachusetts from 2001 to 2013 (n = 629,675). Estimated associations between an IQR increase in ICE for race (0.27) and changes in continuous birthweight along with the 95% confidence intervals are shown. The estimate for the full model is shown in red and the estimates for models omitting the covariate are in black.

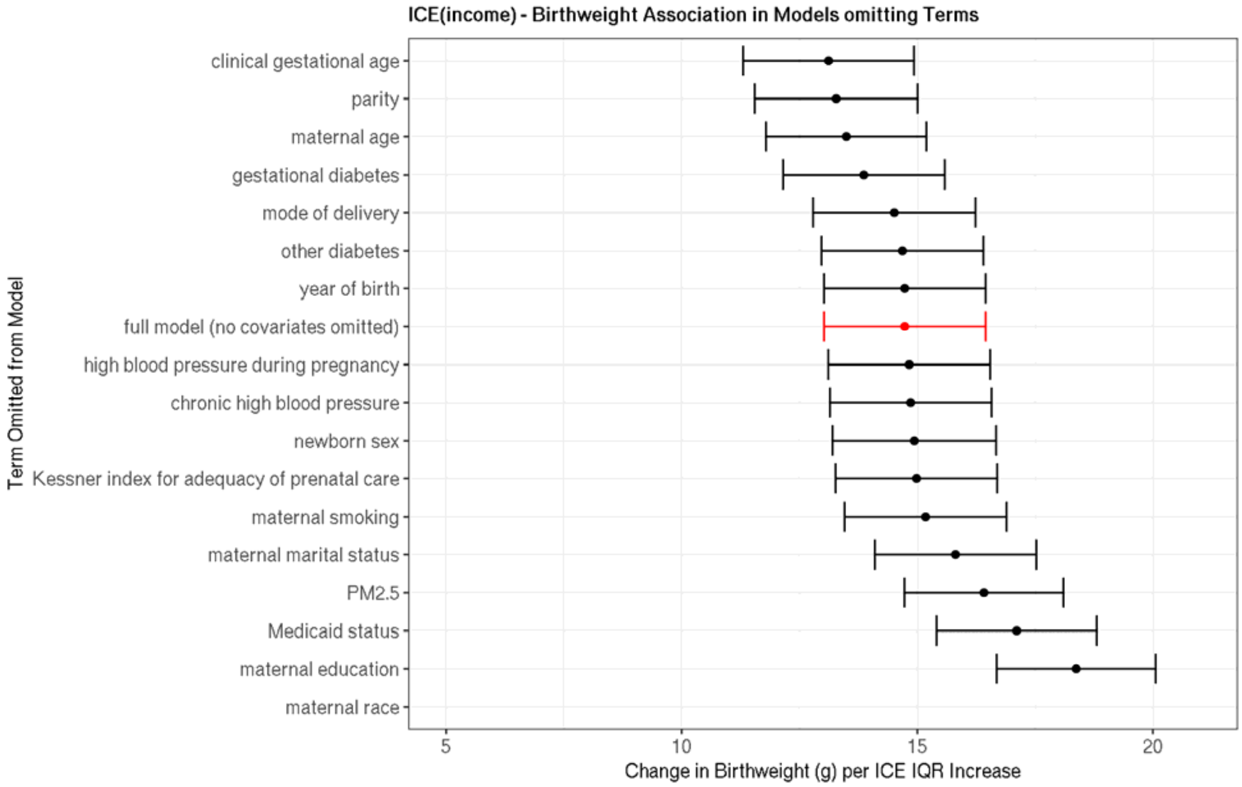

Figure 4-4. Assessment of Confounding by Covariates in the Relationship between Index of Concentration of Extremes (ICE) for Income and Birthweight in Massachusetts from 2001 to 2013 (n = 629,675). Estimated associations between an IQR increase in ICE for income (0.43) and changes in continuous birthweight along with the 95% confidence intervals are shown. The estimate for the full model is shown in red and the estimates for models omitting the covariate are in black.

Discussion

Neighborhood SES, measured by ICE_{race} or $\text{ICE}_{\text{income}}$, was positively associated with continuous birthweight in a large sample of Massachusetts birth records between 2001 and 2013. Associations between increased neighborhood SES and birthweight have also been found in other study settings (Luo et al. 2006; Ncube et al. 2016). However, to our knowledge, there have been no studies that quantified the association between ICE measures and continuous birthweight. Previous analyses have linked ICE measures and adverse birth outcomes such as preterm delivery and birthweight under 2,500 grams (Huynh et al. 2017; Subramanian et al. 2006). Taking a broader view, our finding agrees with prior work that have shown a positive association between ICE measures and better health outcomes such as hypertension, infant mortality, and premature mortality (Feldman et al. 2015; Krieger et al. 2016, 2017b).

The positive association between neighborhood SES and birthweight could be explained by lower psychosocial stress experienced by those living in higher SES neighborhoods. Prior studies have found that areas of higher ICE measures were lower in disorder and violence (Casciano and Massey 2012; Krieger et al. 2017a). In neighborhoods with higher disorder and violence, the stress from having to cope could lead to chronic psychological stress. This, in turn, has been shown to lead to stress, anxiety, decreased metabolic function, and lower general health in the neighborhood's residents (Casciano and Massey 2012; Finch et al. 2010; Shmool et al. 2014). As part of the physiological response to stress, pregnant mothers experience higher levels of catecholamines, which can lead to placental hypoperfusion, resulting in lower oxygen and nutrient delivery to the fetus (Ncube et al. 2016). Other than psychosocial stress, higher birthweights in higher SES neighborhoods could be related to environmental quality. Neighborhoods with higher ICE measures have been found to have lower exposures to lead, lower exposures to noise, lower exposures to airborne black carbon, and higher exposures to surrounding greenness (Casey et al. 2016, 2017, Krieger et al. 2003, 2015). Environmental exposures have been shown to be risk factors for lower birthweight through metabolic and epigenetic pathways (Banay et al. 2017; Basu et al. 2014).

The positive association between neighborhood SES and continuous birthweight was modified by maternal race and Medicaid status. With ICE_{race}, the association between neighborhood SES status and birthweight was weaker among those born to black mothers and those with Medicaid-supported prenatal care (Figure 4-1). The main effects of being born to a black mother or having Medicaid were both negative. In other words, higher birthweight was associated with being born to a white mother and without Medicaid, both indicators of being of higher SES. Moreover, although increased ICE_{race}, an indicator of higher neighborhood SES, was associated with higher birthweight, the associated increase in birthweight was higher among those born to white mothers and those without Medicaid. With $\text{ICE}_{\text{income}}$, the same was not observed; the association between $\text{ICE}_{\text{income}}$ and continuous birthweight was weaker among those born to black mothers but was stronger among those born to those with Medicaid-supported prenatal care (Figure 4-2). Similar to ICE_{race}, the main effects of being born to a black mother or having Medicaid were both negative. But while increased $\text{ICE}_{\text{income}}$ was also associated with higher birthweight, the associated increase in birthweight was higher among those born to white mothers and those with Medicaid. While there are no previous studies that have shown effect modification by maternal race or Medicaid status in the relationship between ICE measures and birthweight, prior studies have suggested that the associations between neighborhood SES and birthweight are modified by maternal race and individual SES (Diez Roux 2001; Pearl et al. 2001). Differences between groups of different individual SES in the health consequences of psychological stress could be due to differences in individual perception (Cohen et al. 1995). In summary, except for how Medicaid status modified the association between ICE_{income} and birthweight, the patterns in association suggest stronger associations between ICE measures and birthweight in those being born to white mothers and without Medicaid, both indicators of higher individual SES.

Our study had strengths and limitations. To our knowledge, this is one of the few studies to apply the ICE to investigate birthweight and the first to demonstrate effect modification by individual SES indicators. The ICE is still seldom-used in epidemiological studies although it has a few advantages over oft-used neighborhood SES measures. As mentioned briefly earlier, the ICE, by describing the concentration of groups on opposite ends of SES, avoids problems that multifactorial indices face when making explicit interpretations. Measures such as a Neighborhood Deprivation Index, which was developed to study birth outcomes and was shown to be positively associated with adverse birth outcomes, incorporate into one measure income, education, employment, housing, and occupation (Messer et al. 2006). Thus, changes in a health outcome associated with changes in a multifactorial index cannot be linked explicitly to one factor. ICE_{race} or ICE_{income}, on the other hand, describes explicitly the concentration of groups of race or income bracket, respectively, allowing us to associate changes in a health outcome specifically to the racial or income demographic makeup of neighborhoods (Feldman et al. 2015). Other strengths of this study include high statistical power, which allowed us to examine effect modification, and multivariate adjustment for many potential confounders, which helped us reach estimates of the association between ICE measures and birthweight independent of many individual covariates. Limitations in our study include misclassification, residual confounding, and limited generalizability. We used the five-year estimates for years 2006-2010 from the American Community Survey to calculate the ICE measures, which could have led to exposure misclassification since as our study population was born in years 2001 to 2013. Neighborhood racial and income demographics could differ throughout the study period but given that 2006-2010 was around the midpoint of the study period and that the five-year estimates are the most stable of the data from the American Community Survey, we expect that the error from this source of misclassification error to be non-differential (U.S. Census Bureau 2017). Exposure misclassification was also possible due to missingness and misreporting of maternal residential addresses but it was unlikely that these were associated with both exposure and outcome. Another limitation in our study was residual confounding. Although we adjusted for many individual characteristics and an environmental exposure in $PM_{2.5}$, our estimates remained confounded by unmeasured confounders. In our assessment of confounding from the included covariates in our final model, we found that we accounted for major sources of confounding (Figure 4-3 and Figure 4-4). Aside from maternal income data, which could more accurately describe individual SES but were not available, we did not expect major changes to our results due to residual confounding. Finally, since our study population were those born to black and white mothers who reported to be living in Massachusetts, the generalizability of our findings is limited to populations that are similar to those living in Massachusetts during the study period. Given the wealth of studies linking increased neighborhood SES with better birth outcomes in United States and abroad, we believe that although the magnitude of associations may differ between our study and future analyses of birthweight using ICE measures, the direction is likely to remain the same.

In a large birth cohort, neighborhood SES, as measured by ICE, was associated with higher birthweight. Maternal race and Medicaid status, indicators of individual SES, modified the association with most evidence suggesting larger benefits among those with higher individual SES. More research into how ICE measures modify associations with health outcomes are needed as this is one of the few epidemiological studies that use this measure of neighborhood SES.

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Conclusions

This dissertation showed evidence of impacts that maternal environmental exposures have on birthweight. First, there was a disparity in how particulate air pollution under 2.5 μm in diameter ($PM_{2.5}$) was associated with birthweight at different points along the birthweight distribution. The negative association was stronger for lighter newborns than for heavier newborns. To fill a research need, I also explored the relative toxicities of four major $PM_{2.5}$ constituents, elemental carbon (EC), organic carbon (OC), nitrate, and sulfate. EC was found to be the most toxic followed by nitrate, OC, and sulfate. In addition to $PM_{2.5}$, I also investigated the effects of surrounding greenness and neighborhood social stress on birthweight. The relationship between maternal residential exposure to surrounding greenness was positive and nonlinear, with stronger associations from low to medium levels of greenness than from medium to high levels of greenness. Measures of neighborhood social stress and privilege, based on concentration of racial and economic groups, were also positively associated with birthweight. Finally, with surrounding greenness and neighborhood social stress and privilege, there was evidence that the relationships were modified by indicators of maternal socioeconomic status.

The results have policy implications. The finding of an environmental disparity in how $PM_{2.5}$ was associated with birthweight can help target those who are most susceptible. The ranking of toxicity for $PM_{2.5}$ constituents informs air pollution control policy. The nonlinearity in the association between surrounding greenness and birthweight can be applied in urban planning and development. More research into how neighborhood social stress and privilege is related to birthweight and other health outcomes is needed.

Taken together, this dissertation highlights that even before birth, one can be susceptible to environmental exposures. Novel exposures such as surrounding greenness and neighborhood social stress and privilege should be considered alongside environmental exposures such as $PM_{2.5}$ in future studies.