Published in final edited form as:

Sci Total Environ. 2019 February 10; 650(Pt 2): 2641–2647. doi:10.1016/j.scitotenv.2018.09.362.

Ambient air pollution and fetal growth restriction: physician diagnosis of fetal growth restriction versus population-based small-for-gestational age

Carrie J Nobles¹, Katherine L. Grantz¹, Danping Liu², Andrew Williams¹, Marion Ouidir¹, Indulaxmi Seeni¹, Seth Sherman³, and Pauline Mendola¹

¹Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD, USA

²Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA

³The Emmes Corporation, Rockville, MD, USA

Abstract

Background: Ambient air pollution may affect fetal growth restriction (FGR) through several mechanisms. However, prior studies of air pollution and small-for-gestational age (SGA), a common proxy for FGR, have reported inconsistent findings.

Objective: We assessed air pollution in relation to physician-diagnosed FGR and population-based SGA in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Consecutive Pregnancy Study (2002-2010).

Methods: Among 50,005 women (112,203 singleton births), FGR was captured from medical records and ICD-9 codes, and SGA determined by population standards for birthweight <10th, <5th and <3rd percentile. Community Multiscale Air Quality models estimated ambient levels of seven criteria pollutants for whole pregnancy, 3-months preconception, and 1st, 2nd and 3rd trimesters. Generalized estimating equations with robust standard errors accounted for interdependency of pregnancies within participant. Models adjusted for maternal age, race/ethnicity, pre-pregnancy body mass index, smoking, alcohol, parity, insurance, marital status, asthma and temperature.

Results: FGR was diagnosed in 1.5% of infants, and 6.7% were <10th, 2.7% <5th and 1.5% <3rd percentile for SGA. Positive associations of SO₂, NO₂ and PM₁₀ and negative associations of O₃ with FGR were observed throughout preconception and pregnancy. For example, an interquartile increase in whole pregnancy SO₂ was associated with 16% (95% CI 8%, 25%) increased FGR

Corresponding author: Pauline Mendola, PhD, Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, 6710B Rockledge Drive Room 3119, MSC 7004, Bethesda, MD 20892, Phone: 301-496-5267, Mobile: 301-905-6118, Fax: 301-402-2084, pauline.mendola@nih.gov.

Declarations of interest: None

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

risk, 17% for NO₂ (95% CI 9%, 26%) and 12% for PM₁₀ (95% CI 6%, 19%). Associations with SGA were less clear.

Conclusions: Chronic exposure to air pollution may be associated with FGR but not SGA in this low-risk population.

Keywords

ambient air pollution; fetal growth restriction; small-for-gestational age

1. Introduction

Fetal growth restriction (FGR), the failure of a fetus to reach its full growth potential, is a condition of pregnancy associated with both short- and long-term morbidity (American College of Obstetricians and Gynecologists, 2013). It can occur when the fetus does not receive adequate nutrients and oxygen from maternal circulation. The exact pathology leading to growth restriction from placenta origin is not exactly known, although it may be associated with inadequate trophoblast invasion and subsequent impaired uterine-placental perfusion as evidenced by growth restriction associated with hypertensive disorders of pregnancy (Mifsud and Sebire, 2014; Salafia et al., 2006). Growth-restriction is associated with a higher risk of stillbirth (Pilliod et al., 2017) and neonatal complications (Pallotto and Kilbride, 2006), as well as long-term outcomes including cognitive delays during childhood (Murray et al., 2015) and development of obesity, type 2 diabetes and cardiovascular disease in adulthood (Crispi et al., 2018; Eriksson et al., 2003). In epidemiologic and clinical research, FGR is often estimated based on small-for-gestational age (SGA), defined as falling below the 10th percentile for birthweight dependent on gestational age. Although FGR and SGA are frequently used interchangeably, they have different meanings. SGA includes constitutionally small but healthy infants and not all infants with FGR will meet criteria for SGA. Distinguishing FGR from SGA remains a pressing challenge in both research and clinical practice (Zhang et al., 2010).

In clinical practice, initial screening for FGR can be accomplished non-invasively using fundal height, the distance from top of the uterus to the pelvic bone, which maps closely with gestational age (American College of Obstetricians and Gynecologists, 2013). When there is a discrepancy in fundal height of more than 3 centimeters, estimated fetal weight <10th percentile based on ultrasound can be used to determine the need for additional screening and management (American College of Obstetricians and Gynecologists, 2013). Fetal growth is also typically monitored with serial ultrasounds in pregnancies at high risk for FGR. Although growth restriction during pregnancy can be managed through early delivery in cases where the intrauterine environment may cause more harm than prematurity (American College of Obstetricians and Gynecologists, 2013; McCowan et al., 2018), there are currently no validated treatment options to improve the flow of nutrients and oxygen to the fetus after diagnosis (Groom and David, 2018). Primary prevention is therefore key to reducing the health effects associated with FGR.

Exposure to ambient air pollution has been associated with both adverse pregnancy events (Pedersen et al., 2014; Siddika et al., 2016) and potential mechanisms underlying the

pathology of fetal growth restriction. As air pollution exposure leads to increases in systemic inflammation and oxidative stress, it may affect fetal growth through various mechanisms including changes in placental volume and blood flow (Hettfleisch et al., 2017), induction of epigenetic changes in placental and fetal tissue (Cai et al., 2017; Kingsley et al., 2016) and alteration of placental mitochondrial content (Janssen et al., 2012).

Prior epidemiologic research evaluating the association of air pollution with growth restriction has been inconsistent. Most studies have employed surrogate assessments for fetal growth, using either SGA or low birthweight (LBW), which may incorrectly classify infants with FGR. While several studies have found an association between ambient air pollution and smaller birthweight (Le et al., 2012; Li et al., 2017; Smith et al., 2017), several other studies have not (Hannam et al., 2014; Lavigne et al., 2016), with little discernable differences in methodologic approaches or magnitude of air pollution exposure. One factor that may contribute to this inconsistency in findings is misclassification of FGR infants by categorizing infants as SGA and/or LBW. To address this potential source of misclassification in prior research, these findings with the association of air pollution with SGA.

2. Methods

The Consecutive Pregnancy Study included 51,086 mothers with two or more deliveries at 20 weeks gestation between 2002-2010 in one of the 20 hospitals within Utah's Intermountain Health Care system. Details of the study have been described elsewhere (Laughon et al., 2014). Briefly, information on demographics, reproductive and prenatal history, current pregnancy and labor and delivery outcomes were abstracted from the antepartum and labor and delivery summary electronic medical records. Each delivery was linked to International Classification of Diseases-9 (ICD9) codes from maternal and newborn discharge summaries. We excluded multiple pregnancies and participants who did not deliver at least two singleton pregnancies.

2.1. Air pollution assessment

Air pollution was assessed for each hospital referral region using modified Community Multiscale Air Quality (CMAQ) models (Foley et al., 2010). Inputs included meteorologic data derived from the Weather Research and Forecasting model, emission data generated from the United States Environmental Protection Agency National Emissions Inventory and photochemical properties of pollutants. Hourly air pollution levels were estimated for seven criteria air pollutants: sulfur dioxide (SO₂), ozone (O₃), nitrogen oxides (NO_x), nitrogen dioxide (NO₂), carbon monoxide (CO), particulate matter <10 microns (PM₁₀) and particulate matter <2.5 microns (PM_{2.5}) and output for 12×12 kilometer grid cells. For grid cells that had monitor data available, CMAQ estimates were fused with inverse-distance weighted monitor data to correct for potential measurement misclassification. To improve precision, merged estimates were weighted to reflect population density within the hospital referral region. Incorporation of inverse-distance weighted monitoring data and weighting for population density significantly improved model performance, with details on model performance published elsewhere (Chen et al., 2014). Briefly, the CMAQ models, which do

not incorporate monitoring data, provide air pollution estimates across the continental United States, even in areas where monitoring was sparse. In model validation, it was found that for several air pollutants, including CO, SO₂ and PM_{2.5}, that CMAQ modeled estimates and averaged ambient air estimates from nearby monitoring stations were different, with fused estimates leading to significant improvements in model performance.

Air pollution estimates were averaged over five windows of exposure: 3-months preconception, whole pregnancy, first trimester, second trimester and third trimester. We additionally assessed a moving 6-week average exposure from 20 weeks gestation through delivery. Finally, to characterize change in air pollution level from the first to the second pregnancy, we characterized air pollution exposure in the first pregnancy as being in the top quartile of exposure (“high exposure”), in the interquartile range (“moderate exposure”) and in the bottom quartile (“low exposure”). We used the same cut-points to characterize “high”, “moderate” and “low” air pollution exposure in the second pregnancy. We then calculated five exposure groups for change in air pollution over time: 1) consistently high exposure (“high” in both the first and second pregnancy), 2) consistently moderate exposure (“moderate” in both the first and second pregnancy), 3) consistently low exposure (“low” in both the first and second pregnancy), 4) increasing exposure (“moderate” in first pregnancy and “high” in second pregnancy, or “low” in first pregnancy and either “moderate” or “high” in second pregnancy), and 5) decreasing exposure (“moderate” in first pregnancy and “low” in second pregnancy, or “high” in first pregnancy and “moderate” or “low” in second pregnancy).

2.2. Small-for-gestational age and fetal growth restriction

Delivery records for birthweight and gestational age were used to calculate birthweight z-scores, based on United States population standards for infant sex (Oken et al., 2003). We classified infants as meeting criteria for SGA <10_{th}, <5_{th} and <3_{rd} birthweight percentile, to evaluate the association of air pollution with differing severities of SGA. The definition of fetal growth restriction was based on physician diagnosis as derived from medical record abstraction and ICD9 codes (656.5 “Poor fetal growth”). The study site provided an overview of their database systems along with a data dictionary to the data coordinating center, where the elements of the data for variables of interest were documented. Prenatal history of intrauterine fetal growth restriction was a predefined category. Although information on criteria used for diagnosis is unknown and likely varied by physician, all hospital sites were part of the same hospital system and utilized a single electronic medical record platform.

2.3. Covariates

Individual-level covariates were abstracted from electronic medical records, and included maternal age (years), race/ethnicity (Latina, non-Latina black, non-Latina white, Asian, other and unknown), pre-pregnancy body mass index (kg/m²), smoking during pregnancy (yes vs. no), alcohol use during pregnancy (yes vs. no), parity (nulliparous vs. parous), insurance type (public vs. private), marital status (married vs. unmarried) and history of asthma (yes vs. no). Hourly ambient temperature (degrees Kelvin) was derived from the

Weather Research and Forecasting model for each hospital referral region and averaged over the same exposure windows used in the assessment of air pollution.

2.4. Statistical methods

Participant characteristics were summarized as means and standard deviations or frequencies and percentages. Air pollution levels were summarized using the median and interquartile range. Correlations between air pollutants were calculated using Spearman correlation coefficients. The outcomes, FGR, SGA <10th, SGA <5th, and SGA <3rd, were analyzed separately for each pollutant and each exposure window. The relative risks of FGR and SGA in association with an interquartile increase in air pollution exposure was estimated by a Poisson binomial regression with a log link (Zou, 2004). The robust standard errors were calculated using generalized estimating equations, accounting for dependence between pregnancies within participant (Diggle et al., 2002).

To further explore the relationship between air pollution and SGA and FGR, we performed several secondary analyses. First, to evaluate whether the association of air pollution with FGR varied by concurrent SGA, we evaluated the relationship between air pollution exposure and three overlapping categories of FGR and SGA: 1) having both FGR and SGA <10th, as compared to those without FGR or SGA <10th; 2) having FGR without SGA <10th, as compared to those without FGR or SGA <10th; and 3) having SGA <10th without FGR, as compared to those without FGR or SGA <10th. Second, to assess whether smoking may modify the association of air pollution with FGR or SGA, we included an interaction term between smoking and air pollution level for the models for FGR and SGA overall. Third, to assess whether air pollution was associated with birthweight overall in addition to low birthweight due to growth restriction, we evaluated the relationship between air pollution exposure and birthweight z-score using generalized estimating equations with an identity link. Fourth, because the length of third-trimester exposure will differ dependent on the length of gestation, we implemented a fetuses-at-risk approach to evaluate exposure over the 6 weeks prior to each gestational week beginning at 20 weeks and odds of delivering an SGA or FGR infant utilizing a discrete-time survival model. We additionally tested for the interaction term between gestational week and air pollution level in the model. Finally, we evaluated whether change in mean air pollution exposure from the first to second pregnancies was associated with risk of FGR and SGA in the second pregnancy, conditional on the occurrence of FGR and SGA, respectively, in the first pregnancy. Using consistently low exposure across the first two pregnancies as the reference group, we evaluated the effect of consistently high, consistently moderate, increasing and decreasing mean exposure to air pollutants across the first two pregnancies. Change-over-time models were additionally adjusted for baseline air pollution level and duration of the interpregnancy interval. Analyses were completed in SAS 9.3 (Cary, NC) and figures created using the ggmap package in R.

3. Results

A total of 50,005 participants contributed 122,203 singleton pregnancies. After exclusion for missing data (2,597 missing data on pre-pregnancy body mass index, 128 on smoking and 283 on alcohol use), we included 109,126 pregnancies in adjusted analyses. In the first

pregnancy of follow-up, participants were on average 25.6 years old (SD 4.5), and the majority were non-Latina white (86.1%), married (86.2%) and had private insurance (73.8%) (Table 1). Approximately half were nulliparous (54.3%), and the majority reported not smoking (97.5%) or drinking alcohol (98.3%) during pregnancy. A total of 1732 (1.5%) pregnancies had infants diagnosed with FGR (see Table A.1). A total of 7809 (7.0%) had infants below the 10th, 2652 (2.4%) below the 5th, and 1312 (1.1%) below the 3rd percentile for SGA. Of those diagnosed with FGR, 1018 (58.8%) were below the 10th, 578 (35.0%) below the 5th and 396 (22.9%) below the 3rd percentile for SGA. In the first pregnancy of follow-up, those with FGR vs. those without were more likely to be unmarried (18.6% vs. 13.7%), have public insurance (30.5% vs. 26.1%), be parous (62.8% vs. 54.1%) and smoke during pregnancy (2.4% vs. 1.7%) (Table 1). Similar differences in demographics were observed for those with SGA versus those without.

Mean air pollution levels generally decreased over the period of follow-up (Table 2). For example, NO₂ decreased from 15.5 (IQR 13.5, 20.9) ppm in the first pregnancy to 15.0 (IQR 12.3, 19.4) ppm in the second pregnancy, and to 13.9 (IQR 10.7, 18.7) ppm among the 10,836 participants with a third observed pregnancy. The most notable decreases were observed for O₃, NO_x, NO₂ and CO. Most air pollutants were positively correlated except for O₃, which was negatively correlated with each of the other pollutants (see Table A.2). NO_x and NO₂ were highly correlated with several other pollutants, including CO ($r=0.92$ and $r=0.87$, respectively) and PM_{2.5} ($r=0.80$ and $r=0.84$, respectively). Air pollution levels were generally consistent across the hospital sites, with no clear difference in whole pregnancy average exposure between the Salt Lake City region and the greater Utah region (Figure A.1).

The proportion of infants born below the 10th percentile for SGA by site ranged from 5.8% to 14.3%. Two hospitals had particularly high rates of FGR (8.2% and 3.6%), although they respectively contributed only 134 (0.3%) and 28 (0.1%) pregnancies and had similarly high rates of SGA (13.5% and 14.3%, respectively). Among the other 18 hospital sites, the proportion with FGR by site ranged from 0.7% to 2.4%.

3.1. Association of air pollution with fetal growth restriction

Air pollution exposure was consistently associated with FGR (Table 3). Across all windows of exposure, SO₂, NO₂ and PM₁₀ were associated with a greater risk of FGR. For example, SO₂ was associated with an 11% (95% CI 1.04, 1.18) higher risk of FGR for first trimester exposure and a 16% (95% CI 1.09, 1.24) higher risk of FGR for third trimester exposure. Conversely, O₃ was consistently associated with a lower risk of FGR, with first-trimester O₃ exposure associated with an 8% (95% CI 0.86, 0.99) lower risk of FGR and third-trimester O₃ exposure a 9% (95% CI 0.86, 0.97) lower risk of FGR. Additional associations of NO_x, CO and PM_{2.5} and higher risk of FGR were observed during preconception and in the third trimester. For example, an interquartile increase in NO_x during preconception was associated with a 23% (95% CI 1.10, 1.38) greater risk of FGR and during the third trimester a 20% (95% CI 1.07, 1.34) greater risk of FGR.

3.2. Association of air pollution with small-for-gestational age

For SGA <10th percentile, we observed few associations for air pollution exposure during preconception, whole pregnancy and trimesters 1 and 2 with SGA apart from ozone, which was associated with a lower risk of SGA during preconception (RR 0.96, 95% CI 0.93, 0.98), trimester 2 (RR 0.97, 95% CI 0.94, 1.00) and whole pregnancy (RR 0.95, 95% CI 0.92, 0.98) (Table 3). However, during the third trimester, we observed a higher risk of SGA <10th percentile per interquartile increase in NOX (RR 1.08, 95% CI 1.03, 1.14), NO₂ (RR 1.05, 95% CI 1.01, 1.10), CO (RR 1.05, 95% CI 1.00, 1.10), PM_{2.5} (RR 1.02, 95% CI 1.00, 1.05) and PM₁₀ (RR 1.03, 95% CI 1.00, 1.06). As with other exposure windows, O₃ exposure in the third trimester was associated with a lower risk of SGA <10th percentile (RR 0.95, 95% CI 0.92, 0.97).

Associations of air pollution exposure with SGA <5th and <3rd percentiles were less clear (see Table A.3). An interquartile increase in O₃ during whole pregnancy was associated with both a lower risk of SGA <5th percentile (RR 0.93, 95% CI 0.88, 0.99) and SGA <3rd percentile (RR 0.89, 95% CI 0.82, 0.97). SO₂ during preconception was associated with a higher risk of both SGA <5th percentile (RR 1.06, 95% CI 1.01, 1.11) and SGA <3rd percentile (RR 1.11, 95% CI 1.04, 1.19). Most air pollutants were associated with a higher risk of SGA <5th and SGA <3rd percentile during the third trimester, although estimates were imprecise.

3.3. Additional analyses

To evaluate whether the association of air pollution with FGR might differ by concurrent diagnosis with SGA, a secondary analysis was performed comparing infants with FGR but without SGA, infants with both FGR and SGA and infants with SGA but without FGR to infants with neither FGR nor SGA. We observed an association between higher air pollution exposure and greater risk of FGR with SGA and FGR without SGA as compared to no FGR or SGA across all windows of exposure (Table 4), consistent with overall findings for FGR. The magnitude of the associations for FGR without SGA were stronger than those for FGR with SGA. For example, an interquartile increase in SO₂ during whole pregnancy was associated with a 25% (95% CI 1.14, 1.37) greater risk of FGR without SGA and a 10% (95% CI 1.01, 1.21) greater risk of FGR with SGA. We observed few associations between air pollution exposure and SGA without FGR, apart from a consistent association of higher O₃ exposure and lower risk of SGA without FGR across all windows.

We additionally evaluated smoking as a modifier of the association of air pollution with FGR and SGA, although there was a low prevalence of smoking (2.8%). We found a general trend of a greater magnitude of adverse effects among non-smokers as compared to smokers (see Table A.4). For example, whole-pregnancy exposure to SO₂ was associated with an 18% increased risk (95% CI 1.10, 1.27) of FGR among non-smokers, but an imprecise 15% decreased risk (95% CI 0.64, 1.12) among smokers. Most significant differences by smoking status were observed during 3-months preconception, particularly for SGA, although the consistent increased risk in FGR with increased air pollution exposure across exposure windows was observed primarily in the non-smoking group who make up 97% of the total study population.

In a secondary analysis to assess whether air pollution may be associated with birthweight overall in addition to low birthweight due to growth restriction, we evaluated the association of air pollution exposure with birthweight z-score. In line with findings for FGR, the air pollutants SO₂, NO₂ and PM₁₀ were consistently associated with lower birthweight z-scores and O₃ was consistently associated with higher birthweight z-scores across all windows of exposure (see Table A.5). Additional associations between higher NO_x and CO in the third trimester and lower birthweight z-score were also observed.

When implementing a fetuses-at-risk approach to evaluate whether the dependency of length of third-trimester exposure on length of gestation may have influenced findings, we observed a similar pattern of association between air pollution exposure and both SGA and FGR as observed for whole third trimester exposure (see Table A.6). For all air pollutants apart from O₃, higher exposure was associated with higher risk of FGR and SGA, although some estimates were less precise. Consistent with findings for the third trimester, an interquartile increase in the 6-week moving average of SO₂, NO_x and PM₁₀ was associated with a 21% (95% CI 1.07, 1.35), 15% (95% CI 1.00, 1.43) and 7% (95% CI 1.00, 1.15) greater odds of FGR, respectively. Additionally, an interquartile increase in the 6-week moving average of NO_x, CO, PM_{2.5} and PM₁₀ was associated with an 11% (95% CI 1.04, 1.19), 6% (95% CI 1.00, 1.12), 4% (95% CI 1.01, 1.07) and 4% (95% CI 1.01, 1.08) greater odds of SGA <10th percentile, respectively. An interquartile increase in the 6-week moving average of O₃ was associated with both a lower odds of FGR (OR 0.95, 95% CI 0.91, 1.00) and SGA <10th percentile (OR 0.96, 95% CI 0.94, 0.98).

Finally, when evaluating the relationship of change in air pollution from the first to second pregnancy and FGR and SGA <10th percentile conditional on prior FGR or SGA, respectively, we observed no clear trends for change in mean air pollution exposure for the entire pregnancy and risk of FGR or SGA <10th percentile in the second pregnancy (see Table A.7).

4. Discussion

We observed that chronic exposure to several air pollutant species, including SO₂, NO₂ and PM₁₀, was associated with a 10-21% higher risk of physician diagnosis of FGR for each interquartile increase in exposure. We did not detect the same chronic exposure results for SGA <10th percentile using a US population birthweight reference, but did observe third trimester associations between air pollution exposure and SGA. In contrast to other pollutants, higher O₃ exposure across all windows of exposure was associated with lower risk of FGR and SGA. These findings suggest that there may be a potential association of chronic air pollution exposure with risk of physician-diagnosis of FGR. Since many studies use birthweight-based measures such as SGA as a proxy for FGR, the subsequent misclassification may make associations more difficult to detect. In our data, more than half of the infants diagnosed with FGR were not classified as SGA.

Air pollution may affect fetal growth through alterations in placentation and establishment of normal blood flow to the fetus. In a study of 229 births between 2011-2014 in Sao Paulo, Brazil, Hettfleisch et al. observed an association between past week exposure to NO₂ and

lower placental vascular index, a measure of relative number of blood vessels, and vascularization flow index, a combination measure of number of blood vessels and flow (Hettfleisch et al., 2017). Air pollution may also affect fetal growth due to decrements in placental mitochondrial content from an increased burden of oxidative stress. For example, prior research has demonstrated an association between PM₁₀ exposure in the third trimester and decrease in mitochondrial content (Janssen et al., 2012) and that changes in mitochondrial DNA mediated 10% (95% CI 6.6, 13.0%) of the association between exposure to NO₂ during whole pregnancy and birthweight (Clemente et al., 2016). Additionally, air pollution may induce epigenetic changes in placental tissue, and has been found to be associated with DNA methylation of long interspersed nucleotide elements (LINE1), a marker for global methylation, in the human placenta (Cai et al., 2017; Kingsley et al., 2016).

Prior studies of the association of air pollution with SGA and LBW have been inconsistent (Ha et al., 2017; Hettfleisch et al., 2017; Lavigne et al., 2016; Le et al., 2012; Li et al., 2017; Smith et al., 2017). For example, using a dispersion model linked to residence to assess the relationship of NO_x, NO₂, O₃, PM_{2.5} and PM₁₀ with SGA and LBW among 671,509 singleton pregnancies in greater London, Smith et al. observed associations between NO_x, NO₂, PM_{2.5} and PM₁₀ with greater risk of both SGA and LBW (Smith et al., 2017). Conversely, using satellite data, land-use regression and interpolation to assess the relationship of NO_x, O₃ and PM_{2.5} with SGA and term LBW among 818,400 singleton pregnancies in Ontario, Canada, Lavigne et al. observed no associations between air pollutants and SGA or term LBW (Lavigne et al., 2016). A number of smaller studies evaluating fetal growth parameters have found more consistent associations with air pollution. In a study of 7,772 singleton births in the Netherlands, van den Hooven et al. observed associations between higher second trimester exposure to PM₁₀ and NO₂ and smaller head circumference at birth, and higher NO₂ exposure in the second and third trimester and shorter birth length (van den Hooven et al., 2012). Similarly, a study by Estarlich et al. among 2,337 singleton births in Spain observed associations of NO₂ with shorter birth length and birthweight (Estarlich et al., 2011). While these findings mirror our findings for an association of air pollution exposure with lower mean birthweight z-score, they suffer from a similar issue as SGA and LBW measures in the inability to distinguish an association between air pollution and the underlying pathology for FGR versus an overall small decrement in birth size. Distinguishing the relationship of air pollution exposure with alterations in the pathology for FGR, as in studies assessing placental blood flow (Hettfleisch et al., 2017), remains an important point for future research.

The unexpected association of higher O₃ with lower risk of FGR and SGA may be explained by the strong inverse association between O₃ and the other air pollutant species assessed. For example, ozone has been shown to increase when traffic-related pollutants are low (McConnell et al., 2006). Due to these negative correlations, higher ozone levels may appear to lower risk but actually reflect the risks associated with lower levels of pollutants that typically scavenge oxygen from ozone.

While this study is novel in evaluating the association of air pollution exposure with a physician diagnosis of FGR, there are several limitations that should be considered when

interpreting our findings. First, air pollution exposure was estimated for the referral region for each hospital of delivery. As compared to estimations of air pollution at a participant's residence, our estimate for the hospital referral region captured a broader daily exposure to air pollution. However, prior research has suggested that area-level estimates of ambient air pollution exposure are similar to estimates accounting for personal monitoring and personal mobility during pregnancy (Ouidir et al., 2015). As any misclassification of individual exposure is likely non-differential and may account for some local mobility around the area where women are likely to live and travel frequently, we anticipate a general bias of findings towards the null. Additionally, we lacked information on indoor exposure to air pollution, including gas stoves and secondhand smoke, and had only a small proportion of women in which to evaluate the interaction of air pollution with maternal cigarette smoking, which limits our ability to evaluate how multiple sources of air pollution exposure may affect FGR and SGA jointly. Although diagnosis of FGR was uncommon and the study lacked information on how the diagnosis was made, the diagnosis of FGR was clearly not the same as identifying an infant with SGA. Although the data were drawn from a single hospital system in which physicians utilized the same electronic medical record platform, there are likely differences between providers in criteria implemented when recording an FGR diagnosis. If these differences were clustered by site, this variation could induce bias. However, the proportion of patients diagnosed with FGR fell mostly within a narrow range, suggesting that this potential threat to validity was likely small. Finally, we calculated relative risks using Poisson regression with a robust variance, a flexible model that may produce very slightly less precise estimates (and subsequent wider confidence intervals) than log-binomial regression, and, as with log-binomial regression, might have fitted probabilities greater than 1 (especially with non-binary outcomes), but these limitations are unlikely to have affected our findings.

5. Conclusion

Our findings highlight the importance of considering the definition of fetal growth restriction in identifying the association of ambient air pollution with pathologies leading to restricted growth. Prior studies have been limited by use of a population standard to assess relative birthweight, which can misclassify constitutionally small infants as growth restricted, and growth restricted infants who are above the 10th percentile for birthweight as healthy. Despite these limitations, combined evidence suggests that air pollution, even at the low to moderate levels found in the United States, may confer a population-wide increased risk for fetal growth restriction, which not only is associated with higher risk of stillbirth and neonatal morbidity (Pallotto and Kilbride, 2006; Pilliod et al., 2017), but has long-term consequences for child development and adult chronic disease risk (Crispi et al., 2018; Eriksson et al., 2003; Murray et al., 2015). Because of the serious health effects of FGR and the potential for the effects of air pollution to be more robust than those currently observed, this remains an important area for future targeted research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Cancer Institute (Consecutive Pregnancy Study Contract Nos. HHSN275200800002I, HH2N27500004 and the Air Quality and Reproductive Health Study Contract No. HHSN275200800002I, Task Order No. HHSN27500008).

Role of the funding source: The funding source had no involvement in the study design; collection, analysis and interpretation of data; writing of the report; or the decision to submit the article for publication.

Abbreviations:

FGR	fetal growth restriction
SGA	small-for-gestational age
LBW	low birthweight
ICD9	International Classification of Diseases-9
CMAQ	Community Multiscale Air Quality Model
SO₂	sulfur dioxide
O₃	ozone
NO_x	nitrogen oxides
NO₂	nitrogen dioxide
CO	carbon monoxide
PM₁₀	particulate matter <10 microns
PM_{2.5}	particulate matter <2.5 microns
IQR	interquartile range
RR	relative risk
CI	confidence interval

References

- American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. *Obstet Gynecol* 2013; 121: 1122–33. [PubMed: 23635765]
- Cai J, Zhao Y, Liu P, Xia B, Zhu Q, Wang X, et al. Exposure to particulate air pollution during early pregnancy is associated with placental DNA methylation. *Sci Total Environ* 2017; 607–608: 1103–1108.
- Chen G, Li J, Ying Q, Sherman S, Perkins N, Sundaram R, et al. Evaluation of observation-fused regional air quality model results for population air pollution exposure estimation. *Sci Total Environ* 2014; 485–486: 563–574.
- Clemente DB, Casas M, Vilahur N, Begiristain H, Bustamante M, Carsin AE, et al. Prenatal Ambient Air Pollution, Placental Mitochondrial DNA Content, and Birth Weight in the INMA (Spain) and ENVIRONAGE (Belgium) Birth Cohorts. *Environ Health Perspect* 2016; 124: 659–65. [PubMed: 26317635]

- Crispi F, Miranda J, Gratacos E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. *Am J Obstet Gynecol* 2018; 218: S869–s879. [PubMed: 29422215]
- Diggle PJ, Heagerty PJ, Liang K-Y, Zeger S. Analysis of longitudinal data: Oxford University Press, 2002.
- Eriksson JG, Forsen TJ, Osmond C, Barker DJ. Pathways of infant and childhood growth that lead to type 2 diabetes. *Diabetes Care* 2003; 26: 3006–10. [PubMed: 14578231]
- Estarlich M, Ballester F, Aguilera I, Fernandez-Somoano A, Lertxundi A, Llop S, et al. Residential exposure to outdoor air pollution during pregnancy and anthropometric measures at birth in a multicenter cohort in Spain. *Environ Health Perspect* 2011; 119: 1333–8. [PubMed: 21429861]
- Foley K, Roselle S, Appel K, Bhawe P, Pleim J, Otte T, et al. Incremental testing of the Community Multiscale Air Quality (CMAQ) modeling system version 4.7. *Geoscientific Model Development* 2010; 3: 205.
- Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. *Am J Obstet Gynecol* 2018; 218: S829–s840. [PubMed: 29229321]
- Ha S, Zhu Y, Liu D, Sherman S, Mendola P. Ambient temperature and air quality in relation to small for gestational age and term low birthweight. *Environ Res* 2017; 155: 394–400. [PubMed: 28258738]
- Hannam K, McNamee R, Baker P, Sibley C, Agius R. Air pollution exposure and adverse pregnancy outcomes in a large UK birth cohort: use of a novel spatio-temporal modelling technique. *Scand J Work Environ Health* 2014; 40: 518–30. [PubMed: 24647593]
- Hettfleisch K, Bernardes LS, Carvalho MA, Pastro LD, Vieira SE, Saldiva SR, et al. Short-Term Exposure to Urban Air Pollution and Influences on Placental Vascularization Indexes. *Environ Health Perspect* 2017; 125: 753–759. [PubMed: 27384326]
- Janssen BG, Munters E, Pieters N, Smeets K, Cox B, Cuypers A, et al. Placental mitochondrial DNA content and particulate air pollution during in utero life. *Environ Health Perspect* 2012; 120: 1346–52. [PubMed: 22626541]
- Kingsley SL, Eliot MN, Whitsel EA, Huang YT, Kelsey KT, Marsit CJ, et al. Maternal residential proximity to major roadways, birth weight, and placental DNA methylation. *Environ Int* 2016; 92–93: 43–9.
- Laughon SK, Albert PS, Leishear K, Mendola P. The NICHD Consecutive Pregnancies Study: recurrent preterm delivery by subtype. *Am J Obstet Gynecol* 2014; 210: 131.e1–8. [PubMed: 24036403]
- Lavigne E, Yasseen AS, 3rd, Stieb DM, Hystad P, van Donkelaar A, Martin RV, et al. Ambient air pollution and adverse birth outcomes: Differences by maternal comorbidities. *Environ Res* 2016; 148: 457–466. [PubMed: 27136671]
- Le HQ, Batterman SA, Wirth JJ, Wahl RL, Hoggatt KJ, Sadeghnejad A, et al. Air pollutant exposure and preterm and term small-for-gestational-age births in Detroit, Michigan: long-term trends and associations. *Environ Int* 2012; 44: 7–17. [PubMed: 22314199]
- Li X, Huang S, Jiao A, Yang X, Yun J, Wang Y, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. *Environ Pollut* 2017; 227: 596–605. [PubMed: 28457735]
- McConnell R, Berhane K, Yao L, Lurmann FW, Avol E, Peters JM. Predicting residential ozone deficits from nearby traffic. *Sci Total Environ* 2006; 363: 166–74. [PubMed: 16095670]
- McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. *Am J Obstet Gynecol* 2018; 218: S855–s868. [PubMed: 29422214]
- Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. *Fetal Diagn Ther* 2014; 36: 117–28. [PubMed: 24577279]
- Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *Bjog* 2015; 122: 1062–72. [PubMed: 25990812]

- Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr* 2003; 3: 6. [PubMed: 12848901]
- Ouidir M, Giorgis-Allemand L, Lyon-Caen S, Morelli X, Cracowski C, Pontet S, et al. Estimation of exposure to atmospheric pollutants during pregnancy integrating space-time activity and indoor air levels: Does it make a difference? *Environ Int* 2015; 84: 161–73. [PubMed: 26300245]
- Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clin Obstet Gynecol* 2006; 49: 257–69. [PubMed: 16721105]
- Pedersen M, Stayner L, Slama R, Sorensen M, Figueras F, Nieuwenhuijsen MJ, et al. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. *Hypertension* 2014; 64: 494–500. [PubMed: 24935943]
- Pilliod RA, Page JM, Sparks TN, Caughey AB. The growth-restricted fetus: risk of mortality by each additional week of expectant management. *J Matern Fetal Neonatal Med* 2017: 1–6.
- Salafia CM, Charles AK, Maas EM. Placenta and fetal growth restriction. *Clin Obstet Gynecol* 2006; 49: 236–56. [PubMed: 16721104]
- Siddika N, Balogun HA, Amegah AK, Jaakkola JJ. Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence. *Occup Environ Med* 2016; 73: 573–81. [PubMed: 27221104]
- Smith RB, Fecht D, Gulliver J, Beevers SD, Dajnak D, Blangiardo M, et al. Impact of London's road traffic air and noise pollution on birth weight: retrospective population based cohort study. *Bmj* 2017; 359: j5299. [PubMed: 29208602]
- van den Hooven EH, Pierik FH, de Kluizenaar Y, Hofman A, van Ratingen SW, Zandveld PY, et al. Air pollution exposure and markers of placental growth and function: the generation R study. *Environ Health Perspect* 2012; 120: 1753–9. [PubMed: 22922820]
- Zhang J, Merialdi M, Platt LD, Kramer MS. Defining normal and abnormal fetal growth: promises and challenges. *Am J Obstet Gynecol* 2010; 202: 522–8. [PubMed: 20074690]
- Zou G A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; 159: 702–6. [PubMed: 15033648]

Highlights:

- Small-for-gestational age (SGA) is a common proxy of fetal growth restriction (FGR)
- We found air pollution increased the risk for physician-diagnosed FGR
- However, SGA was generally not associated with air pollution
- Diagnosed FGR was a more sensitive indicator of risk associated with air pollution
- Studies incorporating SGA may miss risks to fetal growth related to air pollution

Participant characteristics by diagnosis of fetal growth restriction or small-for-gestational age <10th percentile^a in the first pregnancy of follow-up (n=50,005).

	Fetal growth restriction		Small-for-gestational age <10 th percentile	
	Yes (n=827) n (%)	No (n=49,178) n (%)	Yes (n=3,940) n (%)	No (n=46,001) n (%)
Age (years; mean±SD)	24.8±4.7	25.6±4.5	24.9±4.7	25.6±4.5
Race/ethnicity				
Non-Latina white	708 (85.6)	42347 (86.1)	3211 (81.5)	39791 (86.5)
Non-Latina black	8 (1.0)	208 (0.4)	37 (0.9)	179 (0.4)
Latina	88 (10.6)	5240 (10.7)	550 (14.0)	4769 (10.4)
Asian	19 (2.3)	1039 (2.1)	106 (2.7)	951 (2.1)
Other/unknown	4 (0.5)	344 (0.7)	36 (0.9)	311 (0.7)
Marital status				
Married	673 (81.4)	42431 (86.3)	3127 (79.4)	39927 (86.8)
Not married	154 (18.6)	6747 (13.7)	813 (20.6)	6065 (13.2)
Unknown	0	9 (0.02)	0	9 (0.02)
Insurance				
Public	252 (30.5)	12851 (26.1)	1247 (31.7)	11832 (25.7)
Private	575 (69.5)	36327 (73.9)	2693 (68.4)	34169 (74.3)
BMI (kg/m ² ; mean±SD)	22.4±4.7	24.3±5.3	23.6±5.2	24.4±5.3
Parity				
0	519 (62.8)	26608 (54.1)	2575 (65.4)	24510 (53.3)
1	155 (18.7)	11307 (23.0)	759 (19.3)	10692 (23.2)
2	95 (11.5)	6916 (14.1)	388 (9.9)	6615 (14.4)
3+	58 (7.0)	4347 (8.8)	218 (5.5)	4184 (9.1)
Smoking				
Yes	34 (4.1)	1199 (2.4)	209 (5.3)	1023 (2.2)
No	793 (95.9)	47913 (97.4)	3729 (94.6)	44914 (97.6)
Unknown	0	66 (0.1)	2 (0.1)	64 (0.1)
Alcohol use				

	Fetal growth restriction		Small-for-gestational age <10 th percentile	
	Yes (n=827) n (%)	No (n=49,178) n (%)	Yes (n=3,940) n (%)	No (n=46,001) n (%)
Yes	20 (2.4)	828 (1.7)	90 (2.3)	756 (1.6)
No	805 (97.3)	48231 (98.1)	3829 (97.2)	45145 (98.1)
Unknown	2 (0.2)	119 (0.2)	21 (0.5)	100 (0.2)

^aFetal growth restriction was derived from medical records and/or International Classification of Diseases, Ninth Revision (ICD-9) codes; small-for-gestational age <10th percentile was defined as falling below the 10th percentile for birthweight standardized for gestational week and infant sex using a US population birthweight reference.

Table 2.

Distribution of air pollutants across first 3 observed singleton pregnancies

	First pregnancy (n=50,005)	Second pregnancy (n=50,005)	Third pregnancy (n=10,836)
	Median (IQR)	Median (IQR)	Median (IQR)
Sulfur dioxide	1.92 (1.53, 2.26)	1.93 (1.63, 2.20)	1.91 (1.59, 2.19)
Ozone	42.5 (39.4, 44.5)	39.1 (31.3, 42.9)	36.2 (29.3, 41.4)
Nitrogen oxides	30.4 (19.7, 49.5)	26.1 (16.7, 43.0)	23.8 (15.0, 40.5)
Nitrogen dioxide	16.6 (13.5, 20.9)	15.0 (12.3, 19.4)	13.9 (10.7, 18.7)
Carbon monoxide	573 (433, 750)	543 (341, 621)	402 (307, 562)
Fine particulates <2.5 microns	7.52 (6.51, 9.84)	7.54 (6.57, 9.35)	7.39 (6.36, 9.18)
Particulates <10 microns	22.9 (20.1, 26.4)	21.9 (19.3, 24.7)	21.9 (19.4, 24.3)

IQR, interquartile range

Table 3.

Interquartile increase in ambient air pollution and risk of fetal growth restriction and small-for-gestational age birth^a by window of exposure^b

	Whole pregnancy		3 months preconception		Trimester 1		Trimester 2		Trimester 3	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Fetal growth restriction										
Sulfur dioxide	1.16	(1.08, 1.25)	1.15	(1.09, 1.23)	1.11	(1.04, 1.18)	1.13	(1.06, 1.20)	1.16	(1.09, 1.24)
Ozone	0.87	(0.81, 0.94)	0.88	(0.83, 0.94)	0.92	(0.86, 0.99)	0.91	(0.85, 0.97)	0.91	(0.86, 0.97)
Nitrogen oxides	1.12	(1.04, 1.21)	1.23	(1.10, 1.38)	1.09	(0.97, 1.23)	1.14	(1.01, 1.28)	1.20	(1.07, 1.34)
Nitrogen dioxide	1.17	(1.09, 1.26)	1.19	(1.08, 1.31)	1.15	(1.04, 1.27)	1.21	(1.09, 1.34)	1.21	(1.11, 1.33)
Carbon monoxide	1.07	(1.00, 1.15)	1.15	(1.05, 1.26)	1.06	(0.96, 1.16)	1.09	(0.99, 1.20)	1.14	(1.03, 1.27)
Fine particulates <2.5 microns	1.09	(1.02, 1.16)	1.07	(1.02, 1.13)	1.05	(0.99, 1.11)	1.03	(0.97, 1.09)	1.03	(0.99, 1.08)
Particulates <10 microns	1.12	(1.06, 1.19)	1.13	(1.06, 1.21)	1.10	(1.03, 1.18)	1.08	(1.01, 1.15)	1.10	(1.04, 1.17)
Small-for-gestational age <10th percentile										
Sulfur dioxide	1.01	(0.97, 1.04)	1.02	(0.99, 1.05)	1.00	(0.97, 1.03)	1.01	(0.98, 1.05)	1.02	(0.99, 1.05)
Ozone	0.95	(0.92, 0.98)	0.96	(0.93, 0.98)	0.98	(0.95, 1.01)	0.97	(0.94, 1.00)	0.95	(0.92, 0.97)
Nitrogen oxides	1.00	(0.97, 1.04)	1.02	(0.96, 1.08)	0.97	(0.92, 1.03)	1.00	(0.94, 1.06)	1.08	(1.03, 1.14)
Nitrogen dioxide	1.01	(0.97, 1.04)	1.02	(0.98, 1.07)	1.00	(0.95, 1.04)	1.01	(0.96, 1.06)	1.05	(1.01, 1.10)
Carbon monoxide	0.99	(0.96, 1.02)	1.01	(0.97, 1.06)	0.97	(0.93, 1.01)	0.99	(0.95, 1.04)	1.05	(1.00, 1.10)
Fine particulates <2.5 microns	1.01	(0.98, 1.04)	1.00	(0.97, 1.02)	1.01	(0.98, 1.04)	0.99	(0.96, 1.02)	1.02	(1.00, 1.05)
Particulates <10 microns	1.02	(0.99, 1.05)	1.01	(0.98, 1.05)	1.01	(0.98, 1.05)	1.00	(0.97, 1.04)	1.03	(1.00, 1.06)

RR, relative risk; CI, confidence interval

^aFetal growth restriction was derived from medical records and/or International Classification of Diseases, Ninth Revision (ICD-9) codes; small-for-gestational age <10th percentile was defined as falling below the 10th percentile for birthweight standardized for gestational week and infant sex using a US population birthweight reference.

^bModels adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, smoking, alcohol use, parity, insurance type, marital status, history of asthma and ambient temperature.

Interquartile increase in ambient air pollution and risk of 1) fetal growth restriction (FGR) without small-for-gestational age <10th percentile (SGA), 2) FGR with SGA, and 3) SGA without FGR, versus no SGA and no FGR^b, by window of exposure.^a

Table 4.

	Whole pregnancy	3 months		Trimester 1		Trimester 2		Trimester 3	
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	
<i>FGR without SGA</i> <i>(n=713)</i>									
Sulfur dioxide	1.25 (1.12, 1.39)	1.25 (1.14, 1.37)	1.20 (1.10, 1.32)	1.17 (1.06, 1.30)	1.22 (1.10, 1.34)				
Ozone	0.89 (0.80, 0.99)	0.84 (0.77, 0.91)	0.93 (0.84, 1.03)	0.91 (0.83, 1.00)	0.91 (0.83, 1.00)				
Nitrogen oxides	1.14 (1.02, 1.28)	1.35 (1.14, 1.60)	1.18 (0.98, 1.43)	1.14 (0.94, 1.38)	1.15 (0.97, 1.35)				
Nitrogen dioxide	1.21 (1.09, 1.35)	1.37 (1.19, 1.57)	1.23 (1.06, 1.44)	1.24 (1.06, 1.44)	1.23 (1.07, 1.40)				
Carbon monoxide	1.07 (0.97, 1.19)	1.23 (1.07, 1.41)	1.13 (0.98, 1.30)	1.06 (0.91, 1.22)	1.08 (0.93, 1.26)				
Fine particulate matter <2.5 microns	1.09 (0.99, 1.21)	1.13 (1.03, 1.22)	1.05 (0.95, 1.14)	1.05 (0.96, 1.15)	1.03 (0.95, 1.11)				
Particulate matter <10 microns	1.17 (1.07, 1.29)	1.21 (1.09, 1.34)	1.15 (1.04, 1.26)	1.13 (1.02, 1.25)	1.11 (1.02, 1.22)				
<i>FGR with SGA</i> <i>(n=1018)</i>									
Sulfur dioxide	1.10 (1.01, 1.21)	1.10 (1.02, 1.18)	1.05 (0.97, 1.14)	1.10 (1.01, 1.20)	1.13 (1.04, 1.22)				
Ozone	0.86 (0.78, 0.95)	0.91 (0.84, 0.99)	0.91 (0.83, 1.00)	0.90 (0.83, 0.98)	0.91 (0.84, 0.99)				
Nitrogen oxides	1.11 (1.01, 1.23)	1.16 (0.99, 1.35)	1.03 (0.88, 1.20)	1.13 (0.97, 1.33)	1.25 (1.07, 1.45)				
Nitrogen dioxide	1.14 (1.04, 1.26)	1.08 (0.95, 1.22)	1.09 (0.96, 1.24)	1.20 (1.05, 1.37)	1.21 (1.07, 1.36)				
Carbon monoxide	1.07 (0.98, 1.17)	1.10 (0.97, 1.25)	1.00 (0.89, 1.13)	1.11 (0.98, 1.26)	1.20 (1.05, 1.37)				
Fine particulate matter <2.5 microns	1.08 (0.99, 1.18)	1.04 (0.97, 1.12)	1.05 (0.97, 1.13)	1.01 (0.93, 1.09)	1.04 (0.98, 1.11)				
Particulate matter <10 microns	1.09 (1.01, 1.18)	1.08 (0.99, 1.18)	1.08 (0.99, 1.17)	1.04 (0.95, 1.14)	1.10 (1.02, 1.19)				
<i>SGA without FGR</i> <i>(n=6791)</i>									
Sulfur dioxide	0.99 (0.96, 1.03)	1.01 (0.98, 1.05)	0.99 (0.96, 1.02)	1.00 (0.97, 1.04)	1.01 (0.97, 1.04)				
Ozone	0.96 (0.92, 1.00)	0.96 (0.93, 0.99)	0.99 (0.95, 1.02)	0.98 (0.95, 1.01)	0.95 (0.92, 0.98)				
Nitrogen oxides	0.99 (0.95, 1.03)	1.00 (0.95, 1.06)	0.97 (0.91, 1.03)	0.98 (0.92, 1.04)	1.06 (1.01, 1.12)				
Nitrogen dioxide	0.99 (0.95, 1.03)	1.02 (0.97, 1.07)	0.98 (0.94, 1.04)	0.99 (0.94, 1.04)	1.03 (0.99, 1.08)				
Carbon monoxide	0.98 (0.95, 1.01)	1.00 (0.95, 1.05)	0.96 (0.92, 1.01)	0.98 (0.93, 1.03)	1.03 (0.98, 1.08)				

	Whole pregnancy	3 months preconception	Trimester 1	Trimester 2	Trimester 3
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Fine particulate matter <2.5 microns	1.00 (0.97, 1.03)	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)	0.98 (0.96, 1.01)	1.02 (1.00, 1.05)
Particulate matter <10 microns	1.01 (0.98, 1.04)	1.00 (0.97, 1.04)	1.01 (0.97, 1.04)	1.00 (0.97, 1.03)	1.02 (0.99, 1.06)

FGR, fetal growth restriction; SGA, small-for-gestational age; RR, relative risk; CI, confidence interval

^a Models adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, smoking, alcohol use, parity, insurance type, marital status, history of asthma and ambient temperature.

^b Fetal growth restriction was derived from medical records and/or International Classification of Diseases, Ninth Revision (ICD-9) codes; small-for-gestational age <10th percentile was defined as falling below the 10th percentile for birthweight standardized for gestational week and infant sex using a US population birthweight reference.