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Ambient Air Pollution and Adverse Birth Outcomes in Atlanta, 1994-2004

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Ambient Air Pollution and Adverse Birth Outcomes in Atlanta, 1994-2004

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An Abstract of
A dissertation submitted to the Faculty of the Graduate
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of the requirements for the degree of
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Abstract

Ambient Air Pollution and Adverse Birth Outcomes in Atlanta, 1994-2004

In this dissertation, relationships between ambient air pollutants and the adverse pregnancy outcomes of preterm birth and intrauterine growth restriction (IUGR) were investigated in a cohort of approximately 500,000 infants delivered between January 1, 1994 and December 31, 2004 in the five-county Atlanta metropolitan area. Using a time-series approach, daily counts of preterm birth and small for gestational age (SGA), a proxy measure of IUGR, were examined in relation to ambient levels of carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone, PM_{10}, $PM_{2.5}$ and rarely available speciated PM measurements during selected gestational windows of exposure. Daily pollutant levels were characterized using a population-weighted spatial average of air quality monitors in the five-county study area. Measurements from individual monitoring stations were also examined in analyses limited to mothers with residential geocodes within four miles of each station.

Three manuscripts were developed from the work conducted in this dissertation. The first manuscript describes the seasonal patterns of birth in the study population and the potential for confounding by these patterns in temporal investigations of seasonally varying exposures and preterm birth. The methodological issues described motivate the analytic methods utilized in the subsequent manuscripts and are relevant for future temporal studies of seasonally varying exposures in relation to adverse pregnancy outcomes. In the second and third manuscripts, results of the preterm birth and SGA analyses are presented.

Most relationships examined were consistent with little or no association. Preterm birth was associated with nitrogen dioxide in the six weeks before birth and with $PM_{2.5}$ sulfate and $PM_{2.5}$ water soluble metals in the week before birth. SGA was associated with carbon monoxide and coarse PM in the first month of gestation and carbonaceous $PM_{2.5}$ in the final nine weeks of pregnancy, but these associations were only observed in the subset of infants born preterm. Results provide some support for an effect of ambient air pollution on fetal development but should be interpreted with caution given the number of gestational windows and pollutants investigated and lack of strong a priori evidence for an effect of these pollutants.

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CHAPTER 1: INTRODUCTION

Study Motivation

A growing body of evidence suggests that the developing fetus may be susceptible to adverse effects of air pollution. Recent studies reporting a relationship between ambient air pollution and both preterm delivery and intrauterine growth restriction offer reason for concern, particularly because small increases in the prevalence of these adverse birth outcomes have far-reaching public health implications. Four recently published systematic review articles addressing the topic of air pollution and fetal health come to similar conclusions for the specific outcomes examined in this dissertation: the current state of knowledge is insufficient to infer causality but warrants concern and further investigation (Glinianaia et al., 2004; Lacasana et al., 2005; Maisonet et al., 2004; Sram et al., 2005).

Further investigation of air pollution and adverse fetal outcomes is justified given the positive associations reported from previous studies, the uncertainty regarding the critical gestational windows of susceptibility and the inconsistency of specific pollutants implicated. Because of limitations in air monitoring resources, previous investigations have been unable to examine the particle constituents, size fractions and sources which may be driving observed associations between particles and adverse birth outcomes. In fact, previous epidemiologic studies have often reported data for only one or two pollutants or one particle size, raising concern that the pollutant under scrutiny served as a proxy for other pollutants for which data were unavailable. Routine monitoring of $PM_{2.5}$, particles with a diameter 2.5 microns or less, began in the US in 1998 in the wake of increased evidence that many of the health effects observed in association with PM_{10} (particles with diameter 10 microns or less) were attributable to these smaller, respirable size fractions of PM. A thorough investigation of $PM_{2.5}$ is warranted given its known toxicity for other health outcomes and the observed associations between cruder particle measures and these birth outcomes. While $PM_{2.5}$ is now routinely monitored, component

and source characterizations of these particles are rarely available; the Aerosol Research Inhalation Epidemiology Study (ARIES) monitoring station in Atlanta has generated a unique air quality database providing such measurements.

This dissertation examines the relationship between ambient air pollution levels during gestation and the adverse fetal outcomes of preterm birth, intrauterine growth retardation (IUGR) and low birth weight in the five-county Atlanta area over the time period 1994-2004. Atlanta provides an ideal setting to test these hypotheses due to the relatively high air pollution levels and the unusually sophisticated ambient air monitoring networks available. Air monitoring stations provide information on a comprehensive suite of pollutant species, including measures of particulate matter (PM) components since 1998. These measurements allow for the first examination of multiple components and size fractions of PM in relation to these pregnancy outcomes. In addition to using measurements from the monitoring stations, air pollution is characterized using a near-roadway traffic impact assessment, an approach designed to assess the fetal health effects of residential proximity to mobile sources of air pollution. These adverse birth outcomes are further examined in relation to multiple source categories of pollution using the results of air pollution source apportionment conducted by collaborators at the Georgia Institute of Technology.

Study Contribution

A panel convened by the National Research Council for the purpose of identifying high-priority areas for research on health effects of particulate pollution recently concluded that a priority research focus should be on identification of human subpopulations at high risk for adverse effects of air pollution, specifically calling for research on pregnant women and infants (National Research Council, 1998; National Research Council, 1999; National Research Council, 2001). The inter-agency committee planning the National Children's Study has likewise

described the need for research on the impact of air pollution on fetal and children's health (Branum et al., 2003). In a USEPA PM Research Program report released in September 2004, the agency specifically calls for research on PM constituents and sources in relation to adverse health effects, citing the limited availability of monitors for these PM attributes (Gilman, 2004); such measurements are available in Atlanta. Furthermore, several independent reviews of the fetal health and air pollution literature have agreed that the available evidence justifies more research on both preterm delivery and fetal growth in relation to air pollution (Glinianaia et al., 2004; Lacasana et al., 2005; Maisonet et al., 2004; Sram et al., 2005). This dissertation addresses these research needs.

While previous studies have offer provocative evidence of an association between ambient air pollution and adverse birth outcomes, important knowledge gaps remain to be addressed. Identification of the specific pollutant or pollutant constituents responsible for observed associations is critical for causal inference as well as regulatory action. Effective public health policy is most likely to be enacted, and effective, when specific harmful exposures can be identified. The large study population and the extensive air monitoring resources available in Atlanta allow for powerful and refined assessments of many air pollution indices in relation to adverse pregnancy outcomes, including the first assessment of specific particle components. Previous studies differ considerably in the critical gestational windows of susceptibility identified for these birth outcomes. Gestational windows of interest in this dissertation have been identified *a priori* based on the extensive prematurity and IUGR literature. In targeting specific, biologically plausible gestational windows, the specificity of the relationship between air pollution and birth outcomes is further refined. If air pollution and adverse birth outcomes are related, understanding differences in the timing of pollution exposure is critical to risk assessment and management in pregnant women. Given the high level of morbidity and mortality associated with these common adverse birth outcomes, even small increases in risk translate into substantial public health costs.

Other contributions of this study include the first assessment of air pollution sources in relation to these birth outcomes. The identification of pollution sources is particularly useful for regulatory purposes. This study also evaluates the effects of residential proximity to traffic, enabling us to contribute to the growing body of literature on this topic. The retrospective cohort of approximately 550,000 births constitutes the largest investigation to date of air pollution and these reproductive endpoints. The unique air monitoring resources in Atlanta, the public health costs of these adverse birth outcomes, and the specific call for further research on this topic by major US scientific and regulatory agencies constitute a compelling case for the public health rationale and the scientific merit of this epidemiologic investigation.

Study Hypotheses

Primary hypotheses have been formulated through a careful assessment of the fetal health and air pollution literature. Previous studies have exhibited heterogeneity with respect to the pollutants of interest and critical gestational time periods for these outcomes. The following primary hypotheses identify pollutants and gestational windows for which the evidence is most compelling. However, because of the heterogeneity in the existing literature, alternative gestational windows and pollutants are examined in secondary and exploratory analyses.

PRETERM BIRTH

Primary Hypotheses:

- Ambient levels of $PM_{2.5}$, PM_{10}, carbon monoxide (CO) and sulfur dioxide (SO_2) averaged over the last 6 weeks before delivery are associated with the incidence of preterm birth.
- Ambient levels of $PM_{2.5}$, PM_{10}, CO and SO_2 averaged over the last week before delivery are associated with the incidence of preterm birth.

Secondary hypotheses for preterm birth expand the primary hypotheses to include additional pollutants: ozone (O_3), nitrogen dioxide (NO_2), particle components and particle sources. In addition, pollution levels during a secondary gestational window of interest, the first month of gestation, will be examined.

INTRAUTERINE GROWTH RESTRICTION

Primary Hypothesis:

- Ambient levels of $PM_{2.5}$, PM_{10}, and CO averaged over the third trimester are associated with the incidence of intrauterine growth restriction.

Secondary hypotheses for intrauterine growth restriction expand the primary hypotheses to included additional pollutants: O_3, NO_2, SO_2, particle components and particle sources. In addition, pollution levels during the first month of gestation, a secondary gestational window of interest, will be examined. Intrauterine growth restriction (IUGR) will be operationalized using the definition of small for gestational age (SGA); infants in the bottom ten percent for their gestational age, sex, race and parity are classified as SGA.

BIRTH WEIGHT

Primary Hypothesis:

- Ambient levels of PM2.5, PM10 and CO averaged over the third trimester are associated with the incidence of low birth weight (birth weight <2500 grams).

Birth weight, a robust measure of infant health influenced by both intrauterine growth and length of gestation, is examined as a secondary outcome of interest. Additional pollutants (NO_2, SO_2, particle components and particle sources) and an additional gestational window (the first month of gestation) will be examined in exploratory analyses for this outcome.

The primary analytic strategy for all outcomes employs temporal (Poisson) models on aggregated daily counts of premature, intrauterine growth restricted and low birth weight births. A spatio-temporal individual-level analysis is conducted as a secondary analytic approach. To assess these hypotheses, birth outcome data have been obtained from vital records at the Georgia Division of Public Health and linked to ambient pollution levels in the Atlanta area using the state network of monitors, the Georgia Tech $PM_{2.5}$ network and the ARIES monitoring site located in downtown Atlanta. Because $PM_{2.5}$ and particle component data are only available back to 1998, analyses of these pollutants in relation to the birth outcomes of interest will be limited to the 1998-2004 study period.

CHAPTER 2: LITERATURE REVIEW

Preterm Birth

Definitions and subtypes

Preterm birth is defined as birth at less than 37 complete weeks of gestation (259 days); forty weeks gestation is considered to be the normal duration of pregnancy. Obstetric convention designates the first day of the last normal menstrual period as the beginning of pregnancy, despite the fact that fertilization actually occurs an average of two weeks later. Approximately 20 percent of all preterm births are the result of medical interventions, induced by obstetricians because of pregnancy complications or fetal distress. The other 80% are spontaneous events. Spontaneous preterm births can be further divided into preterm birth due to premature onset of labor (50%) and preterm birth due to premature rupture of the chorioamniotic membranes (PPROM) prior to labor (30%) (Alderman et al., 1987; Berkowitz et al., 1998; Mattison et al., 2003).

Epidemiology of preterm birth

Accounting for approximately 12% of all births in the US, preterm birth is a leading cause of infant mortality and morbidity and, even among singletons, has been increasing over the last two decades (McIntire et al., 1999; National Center for Health Statistics, 2004; Wilcox and Skjaerven, 1992). Factors which have previously been observed as predictors of preterm birth include African American ethnicity, preexisting diabetes, infection, lack of or minimal prenatal care, multiple gestation (e.g, twins), physical exertion, hypertension, prior preterm birth, intrauterine growth restriction (IUGR), stress, short cervix, low socioeconomic status, tobacco use, and small body size (Mattison et al., 2003; Gardosi, 2005). Some of these factors have been inconsistently or weakly associated with preterm birth, and less than half of all preterm births can be linked to any identified risk factor. Prenatal care, bed rest, nutritional and antimicrobial

interventions have shown little success at reducing preterm birth (Johnston et al., 2001; Mattison et al., 2003). Some risk factors appear to vary by the degree of prematurity; for example, very preterm births at less than 30 weeks are more likely to be associated with intrauterine infection (Goldenberg et al., 2000). This combined with the multiple subtypes of preterm delivery (i.e. spontaneous labor, spontaneous premature rupture of the membranes and medical intervention) suggest that the cause of premature birth is multifactorial (Berkowitz et al., 1998; Mattison et al., 2003).

Biological Mechanisms

Normal parturition. The onset of labor is a complex, multifactorial process characterized by the initiation of myometrium contractions in the uterus and the dilation of the cervix in preparation for fetal delivery through the birth canal. The specific molecular mechanisms involved are poorly understood, despite the identification of several important maternal, fetal and placental players (Cunningham et al., 2005). Much of what we know about the onset of labor is derived from animal models, which exhibit varying degrees of similarity to the reproductive biology of humans, depending on the species (Elovitz and Mrinalini, 2004). Animal models as well as human data demonstrate a dramatic increase in maternal estrogen levels at the end of pregnancy, shifting the pregnancy environment from progesterone dominant to an estrogen dominant one. The mechanisms by which these maternal endocrine factors influence the timing of delivery is unclear; however, it has been observed that estrogen and progesterone affect the expression of contraction-associated proteins, or CAP genes, which are increasingly expressed as the myometrium is activated and contracts (Mattison et al., 2003). Fetal endocrine factors, such as cortisol released from the fetal hypothalamic-pituitary-adrenal axis (HPA), are also thought to play a role in the initiation of labor, likely through influences on the expression and metabolism of placental prostaglandins, lipid compounds involved in the initiation of uterine contractions (Challis et al., 2005). Corticotropin-releasing hormone (CRH) in placental tissue has recently

been identified as another important endocrine mediator of parturition (Hillhouse and Grammatopoulos, 2002; Wadhwa et al., 2004). Finally, the mechanical stretching of the uterus is thought to play a role in the activation and expression of labor genes, specifically the upregulation of contraction associated proteins (CAP genes) (Lye, 2003).

Preterm birth. The etiologic pathways leading to preterm birth are poorly understood, due in part to the uncertainty surrounding the specific mechanisms of normal parturition. A recent Institute of Medicine workshop on the role of environmental hazards in premature birth outlines three general hypotheses of biological factors thought to contribute to preterm birth: aberrant fetal clock, abnormal implantation and infection/inflammation (Mattison et al., 2003). It should be noted that these hypotheses are not necessarily distinct; for example, inflammatory responses may also be involved in abnormal implantation, and an aberrant fetal clock may be determined by genetic factors governing both implantation and inflammatory processes (Crider et al., 2005; Duc-Goiran et al., 1999).

The hypothesis of an aberrant fetal clock is based on the notion that preterm birth may simply be normal birth occurring early (Roberts, 2003). Controlled animal experiments in which animals have been bred for longer and shorter gestations and embryos from each breed have been implanted into surrogate mothers of the other breed have shown that the fetal genome, as opposed to the maternal genome, determines the length of gestation (Mattison et al., 2003). However, when specific polymorphisms are examined in human populations, genetic factors in both the fetal and maternal genome have been identified in association with the length of gestation (Crider et al., 2005). A related hypothesis introduces the concept of a "placental clock", in which elevated corticotropin-releasing hormone (CRH) levels, well before delivery, correspond to the gradual advancement of the clock toward delivery (Wadhwa et al., 2004).

Implantation of the blastocyst into the uterine wall occurs approximately five days after fertilization and is followed by a dramatic reorganization of blood vessels and changes in the

tissue of the uterine wall establishing uteroplacental circulation (Moore and Persaud, 2003). Very early pregnancy events or exposures which disrupt the implantation and placentation processes may increase the risk of preterm birth (Roberts, 2003). Associations between preterm delivery and various aspects of placental health support this hypothesis. Preterm birth has been associated with markers of low uteroplacental blood flow, as well as measures of placental growth over the course of gestation (Naeye, 1989; Salafia et al., 2005). Furthermore, women with placental abruption, a condition leading to separation of the placenta prior to delivery, are at increased risk of preterm delivery (Ananth et al., 1999b). Hematologic factors affecting blood viscosity have been related to preterm delivery, as well as conditions affecting maternal vascular health such as pre-eclampsia. These observations support the hypothesis that suboptimal placental blood perfusion, caused by abnormal implantation or other factors, may play a role in the etiology of prematurity (Knottnerus et al., 1990; Roberts, 2003).

Hypotheses related to infection and inflammation pathways of preterm delivery are currently receiving the most attention in the literature. Infections localized to the genitourinary tract (e.g., bacterial vaginosis, urinary tract infections), systemic infections (e.g., pneumonia, malaria) and infections localized to other areas of the body (e.g., periodontal disease) have been all been associated with preterm delivery (Elovitz and Mrinalini, 2004; Goldenberg et al., 2000; Hagberg et al., 2005; Jarjoura et al., 2005; Steer, 2005). Intrauterine subclinical infection localized to areas within the uterus, such as the amniotic fluid or the choriodecidual space, appears to be an important player specifically in early preterm births, births at less than 30 weeks (Goldenberg et al., 2000). It may not be microbial agents themselves but an inflammatory reaction which triggers preterm delivery, and recent molecular research has focused on the role of inflammation in the activation of premature uterine contractions and labor regardless of whether the inflammation is caused by infection or other inflammatory insults (Mattison et al., 2003). The association between inflammatory cytokine levels in amniotic fluid and preterm delivery has intensified interest in this hypothesis (Cunningham et al., 2005; Elovitz and Mrinalini, 2004;

Engel et al., 2005a; Hagberg et al., 2005). Reported associations between genetic proinflammatory cytokine polymorphisms and preterm birth as well as history of asthma and preterm birth suggest that differences between individuals in immune response and tissue reactivity may be relevant (Engel et al., 2005a; Sorensen et al., 2003). Preterm delivery can be induced in animal models after administration of various infectious and inflammatory agents such as bacteria or bacteria components, proinflammatory cytokines, and allergic reaction inducing antigens (Bytautiene et al., 2004; Elovitz and Mrinalini, 2004).

Smoking and preterm delivery

Numerous studies have demonstrated a relationship between cigarette smoking during pregnancy and preterm birth, providing sufficient evidence to infer a causal relationship (US Department of Health and Human Services, 2004). In a meta-analysis of 20 prospective studies of maternal smoking and prematurity, the pooled odds ratio comparing smokers to nonsmokers was 1.27 (95% CI=1.21-1.22). When smokers were divided into low (0-10 cigarettes per day), moderate (11-20 cigarettes per day) and high (>20 cigarettes per day) levels of smoking intensity, compared to nonsmokers odds ratios were 1.25 (95% CI=1.12-1.38) for low, 1.38 (95% CI=1.23-1.55) for moderate and 1.31 (95% CI=1.19-1.45) for high, suggesting a dose response between low and moderate, but not moderate and high. The authors suggest that smoking habits of the moderate and high groups may not have been sufficiently differentiated to observe a difference (Shah and Bracken, 2000). Maternal exposure to high levels of environmental tobacco smoke (ETS), or passive smoking, has also been associated with preterm delivery using self report as well as serum cotinine measures to quantify ETS exposure. There is some evidence that this association is stronger in older women (women>30) (Ahluwalia et al., 1997; Kharrazi et al., 2004; Windham et al., 2000). The influence of the timing of smoking during pregnancy is unknown, although one case control study reported that risks of premature rupture of the

chorioamniotic membranes were lower in women who quit smoking during pregnancy compared to women who continued to smoke throughout pregnancy (Harger et al., 1990).

The increased risk of preterm delivery in smokers may be attributable to an increased risk of placenta previa and placental abruption, which are important risk factors for preterm birth and share a dose-response relationship with smoking (US Department of Health and Human Services, 2004). However, at least one study suggests that smoking increases the risk of preterm delivery independent of its effect on these other pregnancy complications. Other manifestations of compromised placental function observed in maternal smokers include placental infarcts, and reduced uteroplacental flow due to vasoconstriction and alterations in collagen production (Ananth et al., 1996; Ananth et al., 1999b; Asmussen, 1980; Naeye, 1978). It has been suggested that these structural changes create a uterine environment more susceptible to increases in intrauterine pressure and contractions (Kyrklund-Blomberg and Cnattingius, 1998). Cigarette smoking has been shown to affect hormone levels and may affect the timing of delivery by interfering with the maternal and fetal endocrine signals involved in parturition (Windham et al., 2005). Smoking may also increase risk of preterm delivery by increasing susceptibility to multiple types of infections through alterations in immune response (Arcavi and Benowitz, 2004).

Air pollution and preterm delivery

The few epidemiological studies investigating ambient air pollution in relation to preterm delivery are suggestive of a small deleterious effect, most consistently with particles. Descriptions and results of studies to date of air pollution and preterm birth are displayed in spreadsheets following this section; the major studies are discussed below.

The first reported evidence of a relationship between premature birth and air pollution in the United States arose from an individual-level analysis in the South Coast Air Basin in Southern California during 1989-1993 (Ritz et al., 2000). Although the South Coast Air Basin covers a

16,000 km^2 area, only maternal residences with a zip code within two miles of one of 17 air monitoring stations were included in the cohort. The investigators examined levels of PM_{10} (particles of less than 10 microns in diameter), carbon monoxide (CO), ozone (O_3) and nitrogen dioxide (NO_2) over 10 gestational windows of exposure using the nearest monitor to assign pollution levels. Using logistic regression models, crude risk ratios showed an association between prematurity and both CO and PM_{10} in the first month of pregnancy as well as the last 6 weeks of pregnancy. PM_{10} in the last 6 weeks, and CO in the first month also demonstrated a dose-response effect across quartiles. After controlling for covariates and other pollutants, only PM_{10} averaged over the last six weeks of pregnancy remained statistically significant with a 19% increase in risk for a 50$\mu g/m^3$ increase in PM_{10} levels. Linear models showed a 0.9 ($\pm$ 0.3) day reduction in length of gestation for a 50$\mu g/m^3$ increase in PM_{10} in the 6 weeks before birth. The elevated risk ratio for PM_{10} in the last 6 weeks of pregnancy remained significant when PM_{10} level in the first month of pregnancy was added to the model. The most important limitation of this investigation is the reliance on spatial contrasts of exposure between difference areas in the greater Los Angeles area. As in any study which utilizes spatial contrasts of exposure, it is possible that results of this study were confounded by some unknown spatially related covariate. For example, smoking prevalence may vary spatially, and in this study maternal smoking was underreported with less than 2% of birth records indicating smoking during pregnancy.

Although results from the study conducted by Ritz and colleagues may have been spatially confounded, a recently published time-series analysis in Pennsylvania provides support for the association reported by Ritz et al., using a temporal approach (Sagiv et al., 2005). All live singleton births in 4 Pennsylvania counties during 1997-2001 were included to form a study population of 190,000 births. Daily mean values using multiple monitors for PM_{10} and SO_2 were calculated separately for each of the counties; pollution levels in the 6 weeks before birth as well as the 1-7 days before birth (1-7 day lags) were examined. Poisson regression mixed effects models included a random intercept for county, splines to control for long term time trends, and

in the acute exposure analysis (1-7 day lags), daily temperature and dewpoint. Investigators found an elevated risk of preterm delivery with increased exposure to PM_{10} and SO_2 in the last 6 weeks of pregnancy (RR per 50μg/m^3 increase in PM_{10}=1.07, 95% CI=0.98-1.18; RR per 15 ppb increase in SO_2=1.15, 95% CI=1.00-1.32). In the quartile analysis, there appeared to be a monotonic dose response for SO_2, but not PM_{10}. However, due to missing data, only 58% of the days had available PM_{10} data. Suggestion of a more acute effect in the few days prior to delivery was also observed for both pollutants. Although this study was analyzed as a time-series, the analysis was not purely temporal. Daily pollutant averages were calculated separately for each county and a random effect term for county was included in the model. The authors choose the counties based on their contrasting PM_{10} and SO_2 distributions. Nevertheless, the results add support for an association between PM_{10} and SO_2 levels at the end of pregnancy and preterm birth.

In Vancouver, a city with pollution levels comparable to many US cities, a positive association between preterm delivery and both SO_2 and CO in the last month of pregnancy was observed (Liu et al., 2003). The 229,085 births in the study population occurred between 1986 and 1998 in the greater Vancouver area (13 census subdivisions, size of study area not reported). A daily average for SO_2, NO_2, CO and O_3 was calculated using multiple monitors across the Vancouver area, and each infant was assigned pollutant values corresponding to their first month, second month, third month, last month and second to last month of gestation. Unfortunately monitoring data were insufficient to evaluate PM. Logistic models indicated that last month CO and SO_2 exposures were related to risk of preterm birth (for 1 ppm increase in CO OR=1.08, 95% CI=1.01-1.15; for 5 ppb increase in SO_2 OR=1.09; 95% CI=1.01-1.19). Control for co-pollutants produced similar effect estimates but decreased precision; exposures in other gestational periods were not controlled. By calculating one daily pollutant value for the entire study area, the authors avoided confounding by spatially varying factors; yet, despite the authors' observation of temporal trends in the outcome, no control for long term time trends was reported. Furthermore,

in the preterm analyses, the authors controlled for birth weight, an outcome which is partially determined by length of gestation.

Characterizations of air quality other than measured ambient levels have been examined in US populations as well. Wilhelm and Ritz looked at maternal residence proximity to roadways in Los Angeles in 1994-1996 as a proxy for exposure to vehicular sources of air pollution (Wilhelm and Ritz, 2003). They reported an increased incidence of preterm delivery with increased proximity to high traffic count roadways. In New Jersey, Vassilev et al., reported increased risk of preterm delivery in census tracts with higher annual levels of polycyclic organic matter (POM), a component of PM, using EPA emissions inventories and atmospheric dispersion modeling to determine annual levels (Vassilev et al., 2001).

Data collected from populations outside the United States in Beijing, Seoul, São Paulo, and the Czech Republic where pollution levels tend to be higher, have also suggested a relationship between preterm birth and PM measures (total suspended particles [TSP] or PM_{10}) as well as gaseous pollutants during pregnancy (Bobak, 2000; Gouveia, 2004; Ha et al., 2003; Xu et al., 1995). In the Czech Republic, Bobak reported an association between preterm delivery and TSP, SO_2 and NO_2 levels during all three trimesters of gestation, although first trimester exposures showed the strongest and most significant effects (Bobak, 2000). Investigators in Beijing were able to take advantage of a government mandated prospective cohort, following all births in 1988 in 4 residential areas of Beijing; pregnant women were required to register with the perinatal health care system within the first three months of pregnancy (Xu et al., 1995). Investigators reported a dose-response relationship between gestational age and a seven day moving average of SO_2 and TSP; they also found that the distribution of gestational age at birth was more skewed toward lower gestational ages on high pollution days. Although this study indicates an acute relationship between ambient air pollution and preterm delivery, it is subject to several limitations which make generalization to US populations difficult. Particulate air pollution was monitored as TSP, a cruder measure of particulate air pollution no longer measured in the

US. Coal stoves are the dominant source of air pollution in this population, where bicycles are the major source of transportation and there are no industrial sources nearby. This suggests a different composition of PM than found in US populations where mobile sources contribute substantially.

Numerous studies suggest that the critical gestational time period for air pollution exposures and preterm birth occurs in late pregnancy. However, several studies, including a subsequent investigation from Los Angeles, have suggested that very early pregnancy may also be a window of susceptibility to air pollution (Bobak, 2000; Liu et al., 2003; Ritz et al., 2000; Wilhelm and Ritz, 2005).

Biological mechanisms and gestational timing. Plausible biological pathways exist for both early and late gestational time windows in relation to preterm birth. Exposures in early pregnancy may disrupt the processes of implantation and placentation and lead to suboptimal placental function. In late pregnancy, infectious or inflammatory pathways may play a role in the initiation of premature labor. Air pollution exposure may play an indirect role in these pathways through its observed alteration of immune parameters (Gardner, 1984; Hertz-Picciotto et al., 2002; Hertz-Picciotto et al., 2004), or may play a more direct role in inflammation-induced preterm delivery. Human airway epithelial cells are known to release pro-inflammatory cytokines in response to airborne particle exposure (Baeza-Squiban et al., 1999; Marano et al., 2002). Furthermore, smaller respirable particles ($PM_{2.5}$) and particle components may enter into circulation and may have similar inflammatory effects on cells in other areas of the body.

Studies of maternal smoking and adverse birth outcomes may offer insight into the biological mechanisms by which ambient air pollution could affect birth outcomes. Alterations in hormone levels, increased susceptibility to infections, compromised placental function, changes in uteroplacental blood flow, and structural changes in uterine tissue have all been observed in

response to cigarette smoke exposure. Exposure to air pollution may involve similar pathways and may further contribute to suboptimal uteroplacental blood flow through hematologic changes such as increased blood viscosity and plasma fibrinogen (related to blood coagulation), responses which have been observed during air pollution episodes (Peters et al., 1997; Seaton et al., 1995).

PREMATURITY						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Bobak, 2000 Czech Republic 1991	Cohort n=108,173	month of birth, SES factors, maternal age, education, parity, infant sex, restricted to singletons	all trimesters	SO2 (50 ug/m3) TSP (50 ug/m3) NOx (50 ug/m3)	**SO2** 1st trimester 1.27 (1.16-1.39); 2nd trimester 1.25 (1.14-1.38); 3rd trimester 1.24 (1.13-1.36) **TSP** 1st trimester 1.18 (1.05-1.31) ; 2nd trimester 1.11 (0.97-1.28); 3rd trimester 1.12 (0.97-1.28) **NO2** 1st trimester 1.10 (1.00-1.21); 2nd trimester 1.08 (0.98-1.19); 3rd trimester 1.11 (1.00-1.23)	mean exposure calculated for each trimester by 24 hr. averages from 67 districts of Czech Republic
Landgren, 1996 Southern Sweden, 1985-90	Ecological n=38,719	year of birth, parity, maternal age	No specific exposure period (general pollution levels)	SO2 (above or below overall annual mean across municipalities) NOx (above or below mean or municipality)	No Effect Odds Ratios were approximately 1 for both **SO2** and **NOx** (comparing high pollution municipalities to low)	*Compared municipalities to each other using annual pollution averages in each municipality * There was stratification by 3 variables within each municipality
Lin et.al., 2001 Taiwan, 1993-1996	Cohort n=543,098	maternal factors, parity, season, infant sex limited to singletons	all pregnancy (residential proximity to source)	SOURCE: petrochemical pollution: those who lived near source compared to those who did not	OR for living in the petroleum refinery area: 1.41 (1.08-1.82)	Compared exposed are vs. a nonexposed area without any air pollution measures
Liu, et. al., 2003 Vancouver, 1986-1998	Cohort, (temporal analysis) n=229,085	month of birth, maternal age, parity, infant sex, gestational age, restricted to singletons	month 1, 2, 3 of pregnancy, the last month and second to last month of pregnancy	SO2 (5ppb) CO(1 ppb) NO2 (10ppb) O3 (10 ppb)	**SO2** OR=1.09 (1.01-1.19) for the last month of pregnancy **CO** OR=1.08 (1.01-1.15) for the last month of pregnancy	PM10: too little data, no effect found, not reported Each woman was assigned the average pollution level in the city over her gestational window (only 1 pollution level calculated per day)
Marzione et. al., 2002 Lithuania 1998	Cohort n=3988	Maternal age, marital status, education, smoking status, season of birth, restricted to singletons	whole pregnancy and by trimester	NO2 (10 ug/m3)	**NO2** OR=1.25 (1.07-1.46) (effects attributable to first trimester exposures)	*Monitoring sites in 12 residential districts used to calculate mean exposures according to residence for trimester

PREMATURITY						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Ritz et. al. 2000, Los Angeles 1989-1993	Cohort n=97,518, women within 2 mile radius of a monitoring station (17 stations total)	maternal age, race, education, parity, birth interval, prenatal care, infant sex, previous preterm/lbw baby, restricted to singletons	whole pregnancy, first month, second month, 1,2,4,6,8,12 and 26 weeks prior to delivery	CO (3 ppb) NO2 (quartile) O3(quartile) PM10 (50 ug/m3)	**PM10** RR_{crude}: 1.20 (1.09-1.33) 6wks before birth (dose response), RR_{crude}=1.16 (1.06-1.26) for first month exposures **CO** RRcrude=1.12 (1.08-1.17)6 wks before birth, RRcrude= 1.04 (1.01-1.09) for first month exposures No effects for **O3** or **NO2** over any periods in single or multiple pollutant models	*Reported the exposure time period for which results were strongest *PM10 crude risk ratios for the 6 weeks before birth held up after control for other pollutants and covariates, PM10 in first trimester and CO risk ratios did not *CO odds ratios were strongest for the inland (not coastal) region
Sagiv, et.al. 2005 Pennsylvania 1997-2001	Time-series (with spatial component) n=187,997	long term trends with LOESS smothers/splines, temperature, dew point, day of week, copollutants, restricted to singletons	6 weeks before birth and 1-7 days lags before birth	SO2 (15 ppb) PM10 (50 ug/m3)	**PM10:** 1.07 (0.98-1.18) 6 weeks before birth; 1.10 (1.00-1.21) 2 days before birth; 1.07 (0.98-1.18) 5 days before birth **SO2**: 1.15 (1.00-1.32) 6 weeks before birth; 1.07 (0.99-1.15) 3 days before birth	*Included 4 Pennslyvania counties, used a mixed effects model with random intercept to account for each county
Vassilev, et.al., 2001 New Jersey 1990-1991	Cohort n=221,406	restricted to singletons, infant sex, previous pregnancy terminations, race, education, prenatal care, smoking, alcohol, urban vs. rural census tract, per capita income	annual averages	Polycyclic Organic Matter (organic compounds) tertiles	High vs. low tertile of **POM**: 1.25 (1.19, 1.31)	*Used modeled estimates of Polycyclic Organic Matter for each census tract using EPA emissions inventories and atmospheric dispersion modeling *Possible effect modification by maternal alcohol use
Wilhelm and Ritz 2003, Los Angeles 1994-1996	Case-Control n≈ 35,000	maternal age, education, infant sex, maternal race/ethnicity, prenatal care, census level income, poverty and housing factors, year, parity, limited to singletons	N/A-general traffic counts over study period	"proximity to traffic" quintiles of distance weighted traffic density daily traffic counts 1994-96	OR=1.08 (1.01-1.15) exposure response relationship noted	For pregnancies with third trimester during fall/winter months for highest DWTD quintile (when air is most stagnant): preterm lbw=1.24 (1.03-1.48) all preterm 1.15 (1.05-1.26) strongest dose response for these women

PREMATURITY						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Wilhelm and Ritz 2005 LA 1994-2000	Cohort n≈100,000 (CO) n≈60,000 (PM10) n≈10,000 (PM2.5)	infant sex, maternal age, race/ethnicity, and education, interval since previous live birth, previous LBW or preterm infant, level of prenatal care, birth season, parity	final 6 weeks 1st trimester	PM10 (10 ug/m3) PM2.5 (10ug/m3) CO (1ppm)	1st trimester: CO 1.04 (1.01–1.07) PM10 0.99 (0.96–1.01) PM2.5 0.73 (0.67–0.80) Last 6 weeks: CO 1.03 (1.00–1.06) PM10 1.02 (0.99–1.04) PM2.5 1.10 (1.00–1.21)	* effects estimates for 1st month of pregnancy were similar to 1st trimester *some of the effects got stronger when the population was limited to near monitor *zip codes included fell >60% within 2 miles of station *Not a lot of PM2.5 data available over time period
Xu et al. 1995, Beijing 1988	Cohort n=25,370 all births in study area in 1988	temperature, humidity, day of week, season, maternal age, gender of child and residential area, restricted to first parity singletons	1-11 days before birth lagged moving average	SO2 (per 100ug/m3) TSP (per 100ug/m3)	**SO2** OR=1.21 (1.01-1.46) for each ln ug/m3 increase, reduction of .075 weeks for each 100ug/m3 increase (7 day lagged moving average) **TSP** OR=1.1 (1.01-1.20) and a reduction of .042 weeks for each increase of 100 ug/m3 (7 day lagged moving average)	*low smoking prevalence *effects larger for younger mothers and in winter (for TSP) *used average of 2 monitoring stations (residents within 5 km of these stations) *gestational age distribution more skewed toward the left on high pollution days vs low
Yang, et.al. 2002 Taiwan 1993-1996	Cohort n=57,127	season, maternal age, marital status, education, gender of infant, restricted to singleton first parity	all pregnancy (residential proximity to source)	SOURCE: petrochemical pollution: those who lived near source compared to those who did not	OR for exposed vs. not exposed 1.18 (1.04-1.34)	compared 16 municipalities in a petrochemical industrial area to 16 reference municipalities

PREMATURITY						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Huynh et al. 2006 California, 1999-2000	Matched case-control n=42,692	maternal age, race/ethnicity, education, marital status, parity	last 2 weeks of pregnancy, first month, all pregnancy	CO (1ppm) PM2.5 (10ug/m3)	**First month:** CO 1.03 (0.93, 1.13) PM2.5 1.13 (1.12, 1.13) **Last 2 weeks:** CO 0.97 (0.90, 1.06) PM2.5 1.06 (1.05, 1.06) **All pregnancy:** CO 0.98 (0.87, 1.10) PM2.5 1.15 (1.15, 1.16)	*Each case matched to 3 full term controls, matched on LMP date, used same gestational window in the controls as cases *County level CO measures, PM2.5 within 5 miles of monitor
Jalaludin et al., 2007 Sydney 1998-2000	Cohort n=123,840	maternal age, indigenous status, sex of infant, parity census defined SES, season	first trimester, last 3 months, last month, first month after conception	PM10 (1 ug/m3) PM2.5 (1 ug/m3) CO (1 ppm) SO2 (1 ppb) NO2 (1 ppb) O3 (1 ppb)	many comparisons made, no consistent patterns, some of the estimates likely biased (e.g., **SO2** autumn RR=6.5 (4.4, 9.6)	*low levels of air pollution *more protective than harmful effects found *used city-wide exposure as well as 5-mile capture areas around monitors
Leem et al., 2006 Korea 2001-2002	Cohort n=52,113	maternal age, education, parity, season, sex	3 trimesters	NO2 (ug/m3) SO2 (ug/m3) PM10 (ug/m3) CO (mg/m3)	**1st trimester:** CO Q4 1.26 (1.11-1.44) PM10 Q4 1.27 (1.04–1.56) NO2 Q4 1.24 (1.09–1.41) SO2 Q4 1.21 (1.04–1.42) ***dose response for NO2, SO2 and CO **3rd trimester:** CO Q4 1.16 (1.01–1.34) NO2 Q4 1.21 (1.07–1.37) ***dose response for CO and NO2	CO, NO2, SO2 exposures were dose dependent *used kriging, spatial and temporal modeling to assign exposure * used log-binomial
Hansen et al. 2006 Brisbane, Australia 2000-2003	Cohort (only temporal contrasts) n=28,200	maternal age, parity, marital status, sex, prenatal visits, SES and type of delivery, indigenous status	first 3 months after LMP, last 3 months before birth (individually and as trimesters)	PM10 (IQR=4.5ug/m3) O3 (IQR=7.1ppb) NO2 (IQR=5.2ppb)	**1st trimester:** PM10 1.15 (1.06–1.25) O3 1.26 (1.10-1.45)	*the PM10 first trimester effect was due to the first month after LMP exposure *there was not potential for spatial confounding *20km radius

Intrauterine Growth Restriction (IUGR)

Definitions and subtypes

Intrauterine growth restriction, or retardation, refers to the failure of a fetus to reach its inherent growth potential. Because it impossible to know an infant's true personal growth potential, growth restricted infants must be identified by comparing measures of growth such as weight or head circumference to population norms. Although preterm infants are often low birth weight (<2500 grams), they may or may not have experienced a restricted rate of growth while *in utero*; a preterm infant may have a weight appropriate for its gestational age or it may be growth retarded as well. In order to separate the two outcomes, which likely have different etiologies (Lang et al., 1996; Villar et al., 1986), researchers have restricted analysis to full-term infants (37-44 weeks gestation) or evaluated birth weight while controlling for gestational age. Intrauterine growth restriction is frequently dichotomized as small for gestational age (SGA), usually defined as birth weight at or below the tenth percentile for infant gender and gestational age. Five percent and fifteen percent thresholds also appear in the literature because it is unclear which threshold best identifies the infants at increased risk of mortality and morbidity while minimizing misclassification of normal, constitutionally small infants. Using any threshold birth weight to define IUGR unfortunately only provides a snapshot of fetal growth, as birth weight is merely the endpoint in the process of fetal growth. In addition, the choice of population used to define the percentile threshold is not straightforward and, in fact, varies across studies (Goldenberg and Cliver, 1997). Because intrauterine growth potential is unknown, any measure of IUGR will be imperfect. The gold standard diagnostic criteria for IUGR is based on multiple ultrasound fetal head, abdominal circumference, and amniotic fluid volume measures over the course of pregnancy; however, these measures are unavailable for examination on the population level in large epidemiological studies. Such measures are often used for diagnosis in pregnancies at high risk of IUGR so that the condition can be monitored and managed before birth (Gabbe, 2002).

The distinction between asymmetric and symmetric subtypes of IUGR suggests multiple etiologic pathways leading to IUGR. To determine whether a newborn exhibits asymmetric vs. symmetric growth restriction, the head-to-abdomen circumference ratio (HC/AC) is used. In asymmetric growth restriction head circumference is normal but abdominal circumference is disproportionately small. Asymmetric growth restriction accounts for approximately two-thirds of all IUGR and is generally thought to be indicative of restricted growth in later pregnancy. Symmetric growth restriction is characterized by proportionally small head and abdomen, and is usually initiated much earlier in pregnancy (Cunningham et al., 2005; Ergaz et al., 2005; Gabbe, 2002). While the subtype of growth restriction may offer clues about the pathophysiology of IUGR, the type of growth symmetry does not necessarily correspond to the timing of insult during pregnancy. For example, suboptimal placentation in very early pregnancy may not affect fetal growth until the third trimester, resulting in an asymmetric IUGR newborn (Cunningham et al., 2005).

Epidemiology of IUGR

Growth retardation, like preterm birth, is an important predictor of infant mortality and morbidity (McIntire et al., 1999; Wilcox and Skjaerven, 1992). Recent observations that intrauterine growth retarded infants are at increased risk for diabetes, hypertension and coronary heart disease later in life magnify the importance of identifying risk factors for this birth outcome in US populations where such chronic health problems are common, disabling and expensive (Barker, 2002; Barker et al., 2002; Petrou et al., 2001).

Risk factors for IUGR include genetic and chromosomal abnormalities in the fetus, congenital infection (toxoplasma, rubella, herpes simplex virus, cytomegalovirus), placental abnormalities (abruption, infarction, smaller placental mass), multiple birth (twins, etc.), poor maternal weight gain, maternal substance abuse (smoking, alcohol, drugs), maternal history of an

IUGR baby, maternal thrombophilia, maternal hypertension, maternal diabetes, maternal hypoxia, maternal anemia, prematurity, and high altitude (Ergaz et al., 2005; Gabbe, 2002).

Biological Mechanisms

Normal fetal growth. Fetal growth during gestation can be divided into three stages. Stage 1, the first 16 weeks of pregnancy, is a period of hyperplasia, when cell number dramatically increases. During this time cellular differentiation and proliferation lead to the establishment of all essential structures in the fetus. Stage 2, weeks 16-32, is characterized by both hyperplasia and hypertrophy; cells are still replicating and increasing in number, but are also growing in size as organ and tissue systems undergo elaboration and growth. Stage 3, from 32 weeks until birth, is dominated by cellular hypertrophy. On average, a fetus gains 5 grams/day at week 15, 15-20 grams/day at week 24, and 30-35 grams/day at week 34. A substantial part of the weight gain late in pregnancy is attributable to fetal accumulation of adipose tissue. In fact, at 29 weeks, fat makes up about 3.5% of fetal body weight, and by 38 weeks fat constitutes 16% of body weight (Gabbe, 2002). Between individuals, rates of fetal growth are more variable in the second half of pregnancy, when the rate of growth is highest and is defined by cellular hypertrophy and fat accumulation (Cunningham et al., 2005; Lin and Santolaya-Forgas, 1998; Moore and Persaud, 2003).

In addition to the fetal genome, which determines growth potential, fetal growth is dependent on the successful transfer of oxygen, glucose, amino acids, fatty acids and the minimization of transfer of harmful substances and metabolic wastes from mother to fetus (Cunningham et al., 2005). The effective transfer of these substrates is governed by both the availability of substrate in the mother as well as effective transfer of substrate across the placenta.

Intrauterine growth restriction. Many of the risk factors for intrauterine growth restriction operate through the impairment of oxygen and nutrient transfer between mother and fetus (Ergaz

et al., 2005). The increased risk of IUGR in mothers with low weight gain during pregnancy, and mothers living at high altitude where oxygen levels are lower demonstrate that fetal growth is affected by maternal intake and supply of substrate. Animal experiments using various mammalian species have also shown that oxygen or nutrient restriction in the mother can impair fetal growth (Schroder, 2003). The lower birth weights observed in births at high altitude are likely attributable to fetal hypoxia, with an average reduction of 102g per 1000 meters of elevation gain reported from Colorado (Jensen and Moore, 1997). This growth restriction due to poor oxygenation at high altitude appears to occur in the third trimester. The effect is less pronounced for women with high-altitude ancestry, suggesting an adaptation to hypoxic conditions over many generations. Further investigation has demonstrated reduced blood flow in the uterine artery and other uterine vessels at high altitude, possibly due to higher fetal blood viscosity as a response to hypoxia (Krampl, 2002). Other evidence also suggests a role for hypoxia in fetal growth restriction. Infants with cardiovascular malformations are likely to be growth restricted, suggesting that fetal circulatory disturbances may limit growth through impaired delivery of oxygenated blood. For example, in infants with tetralogy of Fallot and hypoplastic left heart syndrome, the intracardiac mixing of oxygenated and deoxygenated blood is likely to play a role in growth restriction through suboptimal oxygenation of the fetal blood supply (Rosenthal, 1996). Gestational exposure to carbon monoxide, a gas which competes with oxygen for binding sites on hemoglobin, has been shown to significantly reduced fetal weight in mice (Singh et al., 1993). Animal models also suggest that adverse birth outcomes observed in maternal diabetic pregnancies may operate through hyperglycemia induced hypoxia, with the increased metabolism of glucose decreasing the availability of oxygen and affecting oxygen-dependent gene expression (Li et al., 2005).

Maternal blood parameters are also thought to influence intrauterine growth through alterations in nutrient and oxygen transfer. Maternal thrombophilia, a condition characterized by increased blood coagulation, has been associated with IUGR (Ergaz et al., 2005; Peters et al.,

1997), suggesting that high maternal blood viscosity results in suboptimal placental perfusion. Maternal hematological parameters such as high hemoglobin, hematocrit and erythrocyte counts per volume of blood have also been associated with impaired intrauterine growth, providing additional support for this hypothesis (Knottnerus et al., 1990). Reduced circulating blood volume observed in IUGR pregnancies relative to normal pregnancies provides evidence for the role of reduced uteroplacental blood flow in the etiology of IUGR. Maternal vascular problems, such as those associated with pre-eclampsia, hypertension and diabetes are also likely to operate through this mechanism, with narrowed, constricted blood vessels restricting blood flow through the intervillous space of the placenta (Gabbe, 2002).

In addition to maternal hematological and vascular attributes, any condition affecting the size or function of the placenta will likewise affect the transfer of nutrients between mother and fetus. Placental pathologies such as placental abruption, circumvallate placenta and placental infarction are known risk factors for IUGR (Ananth et al., 1999a; Gabbe, 2002). The vascular development of the placenta itself is critical to developing sufficient nutrient exchange surface area, and can be genetically determined by angiogenesis factor genes as well as influenced by extrinsic factors such as oxygen tension (Kingdom and Kaufmann, 1999; Torry et al., 2004). Animal experiments as well as epidemiological studies indicate that placental mass is a determinant of fetal growth (Gabbe, 2002; Schroder, 2003). In a recent study from North Carolina, investigators found that digitally imaged measures of placental growth during gestation explained 35% of birth weight variance (Salafia et al., 2005). Twins and other multiple gestations provide an interesting example of the role of placental insufficiency in the etiology of IUGR. Monochorionic twins are more likely to be growth restricted than singletons, exhibiting a normal trajectory of growth until week 32 of gestation (earlier for more than two higher order multiples). Placental transfer of substrate is thought to be insufficient to meet the third trimester growth demands of multiple fetuses (Ergaz et al., 2005; Gabbe, 2002).

Inflammatory factors may play a role in intrauterine growth restriction through suboptimal placentation, and subsequent impaired nutrient exchange. Optimal implantation and placentation is dependent on a proper immune response in the maternal uterine tissues to the implanting embryo, and abnormal inflammatory factors may disrupt this process (Duc-Goiran et al., 1999). Polymorphisms governing the production of anti-inflammatory cytokines have been observed in relation to IUGR (Engel et al., 2005b), and there is increasing evidence that pre-eclampsia, a strong risk factor for IUGR, may be a result of suboptimal placentation caused by immune maladaptation in the mother (Sibai et al., 2005).

Genetic syndromes and chromosomal abnormalities often lead to IUGR through alterations in cell replication or congenital malformations. This pattern of IUGR is established early in pregnancy, usually resulting in symmetric growth restriction. Abnormalities in genes governing inflammatory, vascular, hematologic, and placental factors can lead to impaired nutrient exchange as described above and manifest as either symmetric or asymmetric IUGR. Fetal infection is another recognized cause of IUGR. It is thought that infections such as toxoplasma, rubella, herpes simplex virus and cytomegalovirus interfere with cell hyperplasia early in pregnancy (Gabbe, 2002).

Smoking and IUGR

Maternal smoking during pregnancy is a well known cause of intrauterine growth restriction and is widely regarded as one of the most important predictors of birth weight in developed counties (Gabbe, 2002; US Department of Health and Human Services, 2004). The dose response relationship between the number of cigarettes smoked per day and the reduction in fetal growth has been well documented. On average, infants born to mothers who smoked throughout pregnancy weigh 200 grams less than infants born to nonsmokers (US Department of Health and Human Services, 2004). Risk ratios for IUGR range from 1.5 to 2.5, comparing

maternal smokers to nonsmokers (US Department of Health and Human Services, 2004). Maternal exposure to environmental tobacco smoke shows similar, although less pronounced, effects on fetal growth. However, there is disagreement as to the magnitude of the association and the shape of the dose response curve, partly because exposure definition and assessment of ETS varies widely across studies.(Kharrazi et al., 2004; Rubin et al., 1986; US Department of Health and Human Services, 2004; Windham et al., 1999; Windham et al., 2000; Witschi et al., 1997) A meta-analysis of 16 studies of ETS and small for gestational age (or term low birth weight) reported a pooled odds ratio of 1.2 (95% CI: 1.1-1.3) for nonsmoking women exposed ETS during pregnancy compared to nonsmoking women unexposed to ETS during pregnancy; mean birth weight was 28g lower (95% CI=-41, -16) in women exposed to ETS (Windham et al., 1999). The association between exposure to cigarette smoke and reduced fetal growth is also supported by animal experiments (Witschi et al., 1997). The timing and duration of smoking during pregnancy also appears to play a role in the degree of fetal growth restriction. While smoking in any trimester of pregnancy is likely to adversely affect fetal growth, smoking in the third trimester is particularly detrimental. Several studies have demonstrated that smoking cessation before the third trimester dramatically reduces a woman's risk of delivering a low birth weight or small for gestational age baby (Lieberman et al., 1994; MacArthur and Knox, 1988; US Department of Health and Human Services, 2001; US Department of Health and Human Services, 2004). The reduction of birth weight observed in studies of third trimester smokers is consistent with the third trimester concentrated effects observed in high-altitude pregnancies as well as in multiple pregnancies. Furthermore, the third trimester is the period of highest growth demands, with most fetal fat accumulated during this gestational time period.

Several biological mechanisms have been identified to explain the association between maternal active and passive smoking and measures of fetal growth. Compromised uteroplacental blood flow and reduced fetal oxygenation are thought to be two of the most important pathways of smoking induced intrauterine growth restriction (Gabbe, 2002). Carbon monoxide, found in

cigarette smoke as well as ambient air pollution, competes with oxygen binding sites on hemoglobin and effectively lowers blood oxygen carrying capacity. Because the placenta is highly permeable to carbon monoxide, high levels of CO in maternal blood translate into high levels of CO in fetal circulation and therefore lower oxygen availability for fetal tissues (Aubard and Magne, 2000). Cigarette smoking is also associated with specific placental pathologies such as placental abruption and placenta previa as well as more general vascular changes which affect uteroplacental blood flow and subsequent transfer of nutrients from mother to fetus (Ananth et al., 1996; Ananth et al., 1999b; Asmussen, 1980; Naeye, 1978; Salafia and Shiverick, 1999). An increase in maternal blood viscosity and a reduced expansion of plasma volume may also contribute to a decreased rate of uterine artery blood flow and therefore reduced nutrient transfer (Prada and Tsang, 1998). A decrease in immune response in smokers may also increase the risk of growth restriction due to infection (Arcavi and Benowitz, 2004).

Air Pollution and IUGR

Four articles published in 2005 suggest an association between particulate air pollution and reduced intrauterine growth (term low birth weight or SGA); however, these studies are not consistent regarding the gestational window of vulnerability. In Los Angeles, Wilhelm and Ritz found a 36% increased risk of term LBW for a 10 μg/m3 increase in *third trimester* PM_{10} (95%CI=1.12 - 1.65) (Wilhelm and Ritz, 2005). Similarly, Salam et al. reported a reduction in birth weight for *third trimester* PM_{10} exposures (-11 grams per 10μg/m3; 95% CI= -1, -21) (Sram et al., 2005). However, results from Sydney, Australia (Mannes et al., 2005) indicated an effect for *second trimester* PM_{10} (per 10μg/m3 increase OR=1.10; 95% CI=1.00 – 1.48) and $PM_{2.5}$ exposures (per 10 μg/m3 increase OR=1.34 ; 95% CI=1.10-1.63). The fourth study, conducted in California, indicated increased risk for SGA for $PM_{2.5}$ exposures in *all trimesters* (per 10μg/m3 increase OR=1.20, 95% CI=1.07-1.37) (Parker et al., 2005). Previous studies have also implicated particles without showing consistency in the gestational timing of effects (Bobak, 2000; Chen et

al., 2002; Dejmek et al., 1999; Gouveia et al., 2004; Ha et al., 2001; Lee et al., 2003; Wang et al., 1997; Yang et al., 2003). At least one study has reported no relationship between ambient particulate matter and term low birth weight (Maisonet et al., 2001). Some of the differences in results may be attributable to the size fraction of PM monitored ($PM_{2.5}$, PM_{10}, or TSP), the spatial resolution of air quality data, and/or differences in mean levels of PM between study locations. A recent study in Poland using personal air samples from 362 non-smoking women in their second trimester showed that women exposed to higher levels of $PM_{2.5}$ delivered babies with significantly reduced birth weight, shorter birth length and smaller head circumference after controlling for gestational age (Jedrychowski et al., 2004). Molecular studies have observed that particulate air pollution (PM_{10}) is associated with the amount of polycyclic aromatic hydrocarbons (PAH) bound to fetal DNA, and that newborns with higher levels of PAH-DNA adducts exhibit significantly reduced birth weight, birth length and head circumference (Perera et al., 1999; Perera et al., 2003; Perera et al., 1998); however, it is unclear by what specific mechanism fetal DNA damage caused by PAH-DNA adducts could affect fetal growth.

Several studies have shown associations between ambient levels of gaseous pollutants and measures of fetal growth, although results have been less consistent than for PM. Levels of CO during the third trimester have been observed in association with reduced fetal growth in Los Angeles (highest tertile OR=1.22; 95% CI=1.03-1.44) and in the Northeastern US (for 1 ppm OR=1.31; 95% CI=1.06-1.62) (Maisonet et al., 2001; Ritz and Yu, 1999; Wilhelm and Ritz, 2005). Another study from California reported first trimester effects of CO (OR=1.2; 95% CI=1.0-1.4) (Salam et al., 2005). Studies in Denver and in northern Nevada failed to show any association, although the level and range of CO levels in these two locations were relatively modest (Alderman et al., 1987; Chen et al., 2002). Outside the US, several studies have also shown associations between CO levels and reduced fetal growth, most often for exposures in the *first* trimester (Gouveia et al., 2004; Ha et al., 2001; Lee et al., 2003). Other gaseous pollutants, SO_2, NO_2 and O_3, have also been implicated; however, results have been inconsistent in terms of

effect and gestational window (Bobak, 2000; Chen et al., 2002; Gouveia et al., 2004; Ha et al., 2001; Lee et al., 2003; Liu et al., 2003; Maisonet et al., 2001; Mannes et al., 2005; Salam et al., 2005; Wang et al., 1997; Yang et al., 2003). A summary table of the air pollution and intrauterine growth literature is presented at the end of this section.

Biological mechanisms and gestational timing Previous studies of fetal growth in relation to indices of air pollution are inconsistent with respect to the gestational window of susceptibility. However, the well documented relationship between active and passive smoking and reduced birth weight may offer clues to gestational windows of susceptibility as well as biological mechanisms. Many studies of maternal smoking and birth outcomes demonstrate a dramatic reduction in risk of delivering a small for gestational age or low birth weight baby for women who quit smoking by their third trimester of pregnancy. (Lieberman et al., 1994; MacArthur and Knox, 1988; US Department of Health and Human Services, 2001). In fact, women who quit smoking early in pregnancy and nonsmokers deliver infants of similar weights (US Department of Health and Human Services, 1990). The concentration of effects of smoking in the third trimester corresponds to the gestational period of fastest fetal growth.

Ambient air pollution and cigarette smoke may share similar biological mechanisms of reducing fetal growth. Exposure to carbon monoxide may induce fetal hypoxia by increasing carboxyhemoglobin. Air pollution episodes have been observed to increase blood viscosity and plasma fibrinogen (increased coagulation) which may reduce placental blood perfusion by slowing uteroplacental blood flow and providing insufficient support for the massive growth demands of the third trimester (Peters et al., 1997; Seaton et al., 1995). Increased susceptibility to infections after exposure to high ambient levels of air pollution may also play a role in the etiology of IUGR (Hertz-Picciotto et al., 2002; Hertz-Picciotto et al., 2004). Alternatively, abnormal reaction between trophoblast and uterine tissue around the time of implantation may impair placental transfer of nutrients throughout the entire duration of pregnancy (Torry et al.,

2004). Because several studies have observed a relationship between very early gestation PM exposures (first month) and growth restriction, this gestational window also merits examination (Bobak, 2000; Dejmek et al., 1999; Ha et al., 2001).

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Alderman et al., 1987 Denver 1975-1983	Case control n=2870 (998 cases)	gestational age, race, maternal age, education, race, marital status, parity, prior pregnancy loss, delivery interval, month began prenatal care, infant sex	Last 3 months of gestation	CO (quintiles)	**CO:** no effect	examined mean CO level in maternal census tract (54 tracts) during last trimester (w/in 2 miles of monitor) relatively modest range of pollution
Bobak, 2000 Czech Republic, 1991	Cohort n=108,173	sex, parity, maternal age, education, marital status, nationality, month of birth, restricted to singletons	overall pregnancy and by trimester	SO2 (50 ug/m3) TSP (50 ug/m3) NOx (50ug/m3)	**SO2**: 1.27 (1.16-1.39) first trimester; 1.20 (1.11-1.30) overall pregnancy **TSP**: 1.18 (1.05-1.31) first trimester; 1.15 (1.07-1.24) overall pregnancy **NOx**: no effect	IUGR defined as <10th% for gestational age pollution calculated as averaged of 24-hour averages over infants gestation Outcome=SGA (<10th%)
Chen et al., 2002 Northern Nevada, 1991-1999	Cohort n=33,859	restricted to singleton term infants, infant sex, maternal residential city, education, medical risk factors, tobacco, drug and alcohol use, prenatal care, maternal age, race, weight gain	each trimester	CO O3 PM10 (10 ug/m3)	**CO**, **O3** no effect **PM10** : reduction of 11g (2.3-19.8) in third trimester using linear regression, but PM10 not associated using logistic	Used temporal comparison: average concentrations from 8 monitoring stations applied to all mothers for each day relatively low air pollution levels in this area, also high elevation term = gestational age 37 and <44 weeks
Dejmek et al., 1999 Czech Republic 1994-1996	Cohort n=1943	restricted to singletons, smoking, maternal height, prepregnancy weight, education, marital status, year, season, parity	each month of pregnancy	PM2.5 (tertiles) PM10 (tertiles)	**PM10 first month**: high exposure 2.64(1.48-4.71) med exposure 1.62(1.07-2.46) **PM2.5 first month:** high exposure 2.11(1.20-3.70) med exposure 1.26(0.81-1.95)	SGA defined as <10%ile 24-hr values from monitors used to calculate 30-day average exposures for each month of each pregnancy other months did not show an association with PM preterm births excluded

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Dejmek et al., 2000 Czech Republic 1994-1998	Cohort n=4883	limited to term singletons, maternal age, maternal and paternal education, marital status, parity, spontaneous abortion, induced abortion, alcohol, maternal smoking, paternal smoking, ETS, employment of mother and father, long term time trends over the 4 years	months 1-9 of pregnancy	PM10 tertiles PM2.5 tertiles c-PAH (carcinogenic) tertiles	First month (no effects for other months): **c-PAHs:** high (>20 ng/m3) OR=2.15 (1.27, 3.63) medium (2-20 ng/m3) OR=1.60 (1.06, 2.15) **PM10**: high (>50ug/m3) OR=2.14 (1.42, 3.23); medium (40-50 ug/m3) OR=1.44 (1.03, 2.02) **PM2.5**: high (>37 ug/m3) OR=1.96 (1.02, 3.11); medium (27-37 ug/m3) OR=1.38 (0.95, 1.92)	IUGR defined as <10% for gestational week and sex 7 PAHs made up the carcinogenic fraction examined Results were inconsistent in the 2 districts examined (reported results are from Templice) Results were also significant in continuous models
Gouveia, et al., 2004 Sao Paulo, Brazil 1997	Cohort n=179,460	restricted to singletons, gestational age, maternal age, education, infant sex, number of prenatal visits, parity and type of delivery	trimesters	PM10 (quartiles, 10 ug/m3) SO2 (quartiles, 10 ug/m3) NO2 (quartiles, 10 ug/m3) CO (quartiles, 1 ppm) O3 (quartiles, 10 ug/m3)	Low Birth Weight <2500 g: **PM10** (top quartile vs. bottom) 2nd trimester:1.25 (1.03, 1.53) Continuous birth weight: **CO** (for 1 ppm): -23.1g (-41.3, -4.9) first trimester **PM10** (for 10 ug/m3): -13.7 (-27.0, -0.4) first trimester **SO2** (for 10ug/m3): 33.7 (1.6, 65.8) second trimester	all pollutants examined in all trimesters, no other significant associations detected
Ha et al., 2001 Seoul 1996-1997	Cohort/ time series n=276,763	restricted to full term singletons, adjusted for maternal age, education, parity, gender, gestational age, pollution level in other trimester	first and third trimesters	CO SO2 TSP NO2 O3	First trimester exposures for interquartile increase: **CO** RR=1.08 (1.04-1.12) **NO2** RR=1.07 (1.03-1.11) **SO2** RR=1.06(1.02-1.10) **TSP** RR=1.04(1.00-1.08) Third trimester exposures for interquartile increase: **O3** 1.09 (1.04-1.14)	Average daily means average over each infant's first and third trimester (one measure for each day for Seoul) No other effects seen in third trimester

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Jedrychowski et al., 2004 Poland 2001-2003	Prospective Cohort n=362	restricted to nonsmoking women and singletons, parity, prepregnancy weight/height, infant sex, gestational age, season, ETS, education	personal air monitoring period=2 days in the second trimester	PM2.5 (.36.3ug/m3 vs <=36.3ug/m3)	**PM2.5**: birth weight -128.3 g (p=0.03) birth length -0.9cm (p=0.01) head circumference 0.3 cm (p=0.02)	Previous paper discusses study design and exposure in greater detail (Jedrychowski et.al., 2003, IJOMEH) Used log PM2.5 as exposure
Lee et al., 2003 Seoul 1996-1998	Cohort n=388,105	restricted to full term singletons, infant sex, birth order, maternal age, parental education, time trend, gestational age	each month of pregnancy, trimesters	CO PM10 (10 ug/m3) SO2 NO2	First trimester IQR effects: **CO** OR: 1.04(1.01-1.07) Second trimester IQR effects: **PM10** OR=1.04(1.00-1.08) **SO2**=1.06(1.02-1.11) **NO2**=1.03(1.01-1.06)	**CO** exposure in the third trimester found to be protective OR=0.96(0.93-0.99) exposures in months 2-5 (of PM10, SO2, NO2) tended to be strongest in the monthly analyses Used temporal comparisons: 20 stations used to determine daily averages for city of Seoul
Lin, et al., 2001 Taiwan	Cohort n=2545	maternal age, education, parity, marital status, infant sex, season limited to singletons	all pregnancy (residential proximity to source)	SOURCE: petrochemical pollution: those who lived near source compared to those who did not	Exposed vs. unexposed: 1.767 (1.002, 3.116)	Compared individuals living in a petrochemical municipality vs. a nonexposed area (no direct air pollution measures) Study restricted to full term infants (>=37 weeks)
Liu, et al., 2003 Vancouver, 1986-1998	Cohort n=229,085	maternal age, infant sex, parity, gestational age and season of birth, restricted to singletons	month 1, 2, 3 of pregnancy, the last month and second to last month of pregnancy	SO2 (5ppb) CO(1 ppb) NO2 (10ppb) O3 (10 ppb)	**LBW: SO2** OR=1.11 (1.01-1.22) for the first month of pregnancy (LBW) **IUGR**: Associated with **SO2, NO2** and **CO** levels in first month. (OR for three pollutants ranged from 1.05-1.07)	PM10: too little data, no effect found, not reported Used temporal comparison: Each woman was assigned the average pollution level in the city over her gestational window (only 1 pollution level calculated per day) This study looked at LBW controlled for gestational age and IUGR

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Maisonet et al., 2001 Northeastern US 1994-1996	Cohort n=89,557	gestational age, gender, parity, maternal age, race, marital status, prenatal care, smoking and alcohol use, weight gain, previous terminations, season, other pollutants, restricted to term singletons	trimester and overall pregnancy	CO (1 ppm) PM10 SO2 (quartiles)	**CO** OR=1.31 (1.06-1.62) in third trimester **SO2** suggestion of effect in second trimester, but not consistent and no dose-response **PM10**: no effect	Average of daily means in each of 6 cities applied to each trimester
Mannes, et al., 2005 Sydney, Australia 1998-2000	Cohort n=138,056	infant sex, maternal age, gestational age, maternal smoking, first prenatal visit > or < 20 weeks, race, primiparity, season of birth, SES restricted to singletons	trimesters	CO (1 ppm) PM10 (1 ug/m3) PM2.5 (1 ug/m3) O3 (1ppb) NO2 (1ppb)	*SGA 2nd trimester* **PM10** 1.01 (1.00-1.04) **PM2.5** 1.03 (1.01, 1.05) **O3** 1.01 (1.00, 1.01) *SGA 3rd trimester:* **NO2** 1.01 (1.00, 1.02)	Small for gestational age: more than 2 standard deviations below the mean national birth weight for a given gestational age Air pollution levels were relatively low in Sydney In continuous birth weight models **CO, NO2** and **PM10** were associated with reduced birth weight (2nd and 3rd trimesters)
Parker, et al., 2005 California 2000	Cohort n=18,247	restricted to gestational age=40 weeks maternal race, age, education, marital status, parity, other pollutant (either PM2.5 or CO) restricted to singletons	trimesters, overall pregnancy	CO (quartiles) PM2.5 (quartiles)	Overall pregnancy , SGA: **CO** (top quartile vs. bottom) SGA: 0.82 (0.68, 0.99) **PM2.5** (top quartile vs. bottom): 1.23 (1.03-1.50) Continuous birth weight: **CO** (top quartile vs. bottom): -36.1g (-16.5g, -55.8g) **PM2.5** (top quartile vs. bottom): 2.6 (-20.6, 25.8) results were similar in all trimesters	only mothers who lived within 5 miles of a monitor were included results were similar across trimesters Small for gestational age defined as less than 2872g for girls and less than 2986g for boys
Perera, et al., 1998 Poland, 1992	Prospective cohort n=160	maternal height, age, education, history of lbw, alcohol consumption, gestational age, infant sex, parity, plasma cotinine (smoking)	biomarkers measured at birth	PAH-DNA adducts above median level vs. below at birth	Infants above the median had a decrease in birth weight of 147g (p=0.05), decrease in birth length of 1.1cm (p=0.02) and a decrease in head circumference of 0.9cm (p=0.005) Continuous models showed reduced birth weight and length but p>0.05	Elsewhere they demonstrate that infants receive a higher biologic dose of PAHs relative to mothers (see *Perera, et.al., 1999 EHP*) Could not assess timing of exposures, as exposure (PAH-DNA adducts) were measured in the infants at birth

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Perera, et al., 2003 New York	Prospective cohort n=263 African American and Dominican women	BMI, parity, maternal age, cotinine, infant sex, gestational age	personal air samples during 2 days of each woman's third trimester	PAHs (particle and vapor form) above and below median	In African American women: high **PAH** exposure associated with reduced birth weight (p=0.003) and smaller head circumference (p=0.01) but not birth length (p=0.3). No effects observed in Dominican women.	They included models adjusted for plasma chlorpyrifos (CPF) which is a measure of organophosphate pesticide exposure
Ritz and Yu 1999 Los Angeles 1989-1993	Cohort n=125,573	restricted to term singletons, maternal age, prenatal care, ethnicity, education, commuting habits in the monitoring area	third trimester	CO (tertiles)	**CO** OR=1.22 (1.03-1.44) for 3 month average exposure >5.5 ppm in 3rd trimester	mothers were within 2 mile radius of a station Outcome=term low birth weight (gestational age 37-44 weeks) No effect for other trimesters Stronger effects for younger women (<20 years) and higher parity women
Salam, et al., 2005 California, 1975-1987	Cohort n=3901	smoking, maternal race, SES variables, maternal age, birth interval, parity, marital status, gestational diabetes, season (splines), elevation, temperature	trimesters and overall pregnancy	O3 (12 ppb) NO2 (25 ppb) CO (1.4 ppm) PM10 (20 ug/m3)	*Continuous birth weight:* **O3:** 47.2 (27.4, 67.0) g decrease (robust for 2nd and 3rd trimesters) **CO:** 21.7 (1.1, 42.3) g decrease (1st trimester) **PM10**: 21.7 (1.1, 42.2) g decrease (3rd trimester, disappeared after control for O3) *IUGR:* **CO** in 1st trimester and **O3** in 3rd trimester OR=1.2 (p<0.05)	IUGR defined as <15th percentile for gestational age and sex air pollution assigned using zip codes a linear, quadratic and cubic terms were included in the model to account for gestational age which has a nonlinear relationship with birth weight
Vassilev, et al., 2001 New Jersey 1990-1991	Cohort n=221,406	limited to term singletons, examined infant sex, previous pregnancy terminations, race, education, prenatal care, smoking, alcohol, urban vs. rural census tract, per capita income	annual averages	Polycyclic Organic Matter (organic compounds) tertiles	High vs. low tertile of **POM**: Very low birth weight: 1.31 (1.15, 1.51) lbw in term births: 1.31 (1.21, 1.43)	Used modeled estimates of Polycyclic Organic Matter for each census tract using EPA emissions inventories and atmospheric dispersion modeling Possible effect modification by maternal alcohol use

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Wang et al. 1997, Beijing 1998-1991	Prospective cohort n=74,671	gestational age, residence, year of birth, maternal age, infant sex, restricted to first parity	trimesters, overall	SO2 (100 ug/m3) TSP (100 ug/m3)	**SO2** OR=1.11(1.06-1.16) third trimester **TSP** OR=1.10(1.05-1.14) third trimester	Average of daily means from 2 monitoring stations in city applied to each trimester TSP and SO2 effects were difficult to separate very low smoking rate in this population
Wilhelm and Ritz 2005, Los Angeles 1994-2000	Cohort 653 cases, 10,160 noncases women within 1-4 miles of a monitoring station	restricted to term singletons, maternal age, race, education, parity, level of prenatal care, infant sex, previous preterm or lbw baby, birth season, other pollutants	first trimester and last 6 weeks of pregnancy	"Primary Exhaust Particles" CO (1 ppm) PM10 (10 ug/m3)	For women within 1 mile of a station: **CO**: 1.21 (0.85, 1.74) third trimester (multipollutant models within 1 mile of monitor) **PM10**: 1.36 (1.12, 1.65) third trimester (multipollutant models within 1 mile of monitor)	Effects were smaller for women further away than 1 mile from a station Not a lot of PM2.5 data available over time period
Wilhelm and Ritz, 2003 Los Angeles 1994-1996	Case-Control n≈ 30,000	restricted to term singletons maternal age, race, education, prenatal care, infant sex, census level factors (median household income, etc.)	none-general traffic counts over study period	"proximity to traffic" quintiles of distance weighted traffic density daily traffic counts 1994-96	OR for highest quintile 1.14 (1.00-1.29) For mothers whose third trimester was in fall/winter months (when air is most stagnant): OR=1.39, (1.16-1.67)	exposure response not consistent Outcome=term low birth weight
Williams et al. , 1977 Los Angeles 1973	Cohort n=424	smoking status, SES, age, antenatal care, prepregnant weight, weight gain, sex, gestational length, parity	trimester and overall pregnancy	combined heavy, intermediate, or light pollution classification using NO2, O3 and CO	314 gram reduction in birth weight observed when comparing heavily polluted zones to light pollution zones p<.01	examined women near highest pollution level monitors versus those near lower pollution monitors controlled for gestational age
Yang et al., 2003 Taiwan 1995-1997	Cohort n= 13,396	restricted to term first parity singletons season, infant sex, maternal age, marital status, education	each trimester	SO2 (1 ug/m3) PM10 (1 ug/m3)	**SO2** 0.52 (0.09-0.63)g reduction in birth weight for 1 unit increase in first trimester **PM10** 0.52 (0.19-0.85) g reduction in birth weight for 1 unit increase in first trimester	6 monitoring sites, residences within 2 km of a station assigned average of daily means for each trimester no effects for other trimesters

IUGR (SGA or LBW controlled for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Bell et al., 2007 MA and CT 1999-2002	Cohort n=358,504	gestational age, prenatal care, type of delivery, sex, birth order, weather, year mothers race education, marital status age and tobacco use	trimesters, pregnancy	PM10 (7.4 ug/m3) PM2.5 (2.2 ug/m3) CO (303 ppb) SO2 (1.6 ppb) NO2 (4.8 ppb)	Pregnancy: NO2 -8.9 g (-7.0, -10.8) CO -16.2g (-12.6, -19.7) PM10 -8.2g (-5.3, -11.1) PM2.5 -14.7g (-12.3, -17.1) for LBW: NO2 1.03 (1.00-1.05) PM2.5 1.05 (1.02-1.09)	average county level exposure assigned trimester specific analyses showed negative associations between birth weight and PM10 (3rd), CO (1st and 3rd), NO2 (1st), SO2 (1st), PM2.5 (2nd, 3rd) <32 weeks excluded
Hansen et al., 2007 Brisbane, Australia 2000-2003	Cohort n=26,617	gestational age (quadratic term), sex, mothers age, parity, indigenous status, prenatal care, SES, marital status, previous abortions or miscarriages, type of delivery	trimesters, months of pregnancy	PM10 bsp (visibility reducing particles) O3 NO2	no effects reported for birth weight or SGA (<10% for age and sex) a reduction in crown heel length was associated with third trimester NO2 levels	linear and logistic models run city-wide exposure metric used (no spatial confounding) limited to term births low levels of pollution reported

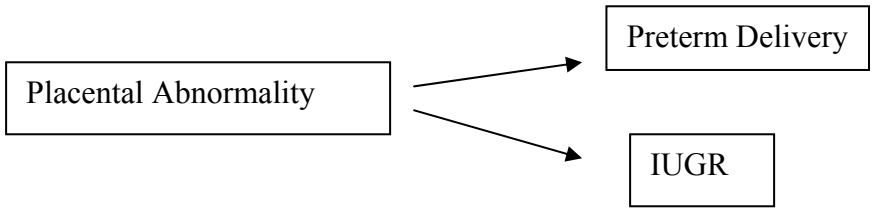
Low Birth Weight (without control for gestational age)						
Citation Location/ Time period	***Type of study Sample Size***	***Covariates***	***Exposure period***	***Pollutants (unit)***	***Effect Estimates 95% CI's***	***Additional findings/Notes***
Bobak and Leon, 1999 Czech Republic 1986-88	Ecological n=223,929	adjusted for SES factors (at district level) and other pollutants	none-annual means	TSP (50ug/m3) SO2 (50ug/m3) NOx (50ug/m3)	**SO2**=1.10 (1.01-1.20) **NOx**=.99 (.89-1.10) **TSP** 1.03 (.95-1.11)	TSP=80% PM10 in study area Exposure=annual mean in each of 45 districts
Bobak, 2000 Czech Republic, 1991	Cohort n=108,173	sex, parity, maternal age, education, marital status, nationality, month of birth restricted to singletons	trimester and overall pregnancy	SO2 (50 ug/m3) TSP (50 ug/m3) NOx (50ug/m3)	**SO2**: significant OR>1 all trimesters, disappeared when controlled for gestational age **TSP**: significant OR>1 all trimesters, disappeared when controlled for gestational age **NOx**: no effect with or without gestational age control	No effects after control for gestational age mean exposure calculated for each trimester by 24 hr. averages from 67 districts of Czech Republic
Landgren, 1996 Southern Sweden, 1985-90	Ecological n=38,719	year of birth, parity, maternal age	none-annual means	SO2 (above or below overall annual mean across municipalities) NOx (above or below mean or municipality)	**NO EFFECT** Odds Ratios were approximately 1 for both **SO2** and **NOx** (comparing high pollution municipalities to low)	*Compared municipalities to each other using annual pollution averages in each municipality * There was stratification by 3 variables within each municipality
Marzione et al., 2002 Lithuania 1998	Cohort n=3988	Maternal age, marital status, education, smoking status, season of birth, restricted to singletons	whole pregnancy and by trimester	NO2 (10 ug/m3)	overall pregnancy for highest tertile: **NO2** OR=1.54 (0.80-2.96) (effects attributable to first trimester exposures)	*Monitoring sites in 12 residential districts used to calculate mean exposures according to residence for trimester
Rogers, et al., 2000 Georgia, USA 1986-1988	Case-Control n=143 cases, 202 controls	maternal race, age, education, weight gain, prepregnancy weight, toxemia, alcohol or drug use, cigarette smoke, stress, prenatal care, income, infant gender, parity	none-annual means	TSPSO2 (combined metric)	Compared to <9.9 ug/m3 **TSPSO2** 9.9-25.1 ug/m3: 0.99 (0.51, 1.72) 25.2-56.8 ug/m3: 1.27 (0.68, 2.37) >56.8 ug/m3: 2.88 (1.16, 7.13)	cases were VLBW infants (<1500g) and controls weighed >2500g annual means of pollution at maternal residences were modeled using a gaussian plume atmospheric transport model most vlbw infants were also preterm

Causal Relationships between Preterm Birth and IUGR

Preterm birth and intrauterine growth restriction are not independent health outcomes, therefore any investigation of these outcomes in relation to a common exposure must carefully consider possible causal relationships between the outcomes. Intrauterine growth restriction is a recognized risk factor for premature delivery, and when diagnosed *in utero* using ultrasound, is a common motivation for medical induction of preterm birth (Fang, 2005). A recent multicenter study in 16 European counties demonstrated that both spontaneous preterm births (OR=1.51; 95% CI=1.33-1.71) and medically induced preterm births (OR=6.38; 95% CI=5.47-7.45) were more likely to be small for gestational age than term infants. Small for gestational age (SGA) in this study was defined using the distribution of estimated fetal weights at each gestational age for gestations which proceeded to normal term delivery, as opposed to the more common definition which is based on the live birth weights of all infants at a given gestational age. The association between IUGR and preterm birth also varies by degree of prematurity; births at less than 34 weeks are the most likely to be growth restricted (Bukowski et al., 2001; Gardosi, 2005; Zeitlin et al., 2000).

The relationship between the two adverse birth outcomes may be due to shared risk factors or one outcome may be on the causal pathway to the other. An example of the first possibility is displayed in causal diagram 1; placental abnormalities may independently increase the risk of preterm birth and IUGR.

Causal Diagram 1.



Alternatively, IUGR may be on the causal pathway from placental abnormality to preterm birth. Some have speculated that preterm birth may be a fetal response to a suboptimal uterine environment, such as in the case of IUGR (Gardosi, 2005).

Causal Diagram 2.

Causal diagram 2 certainly applies to the case of *induced* preterm births which have been medically indicated specifically because of IUGR diagnosis *in utero*. While the above diagrams illustrate possibilities for the nature of the relationship between IUGR and *spontaneous* preterm delivery, the true relationship between the two outcomes is unclear and deserves careful consideration in the analysis and interpretation of results. Analytic techniques and considerations of this possibility are discussed below in the methods section.

Air Pollution

Ambient air pollution consists of primary pollutants, emitted directly into the air from sources, and secondary pollutants, products of chemical reactions occurring in the atmosphere. As a general rule, secondary pollutants are more spatially homogeneous than primary pollutants. Meteorological conditions such as wind, temperature, sun, humidity and rain influence the dispersion, diffusion and chemical and physical reactions between pollutants in the atmosphere and consequently have a tremendous impact on ambient air pollution levels (McGregor, 1999). Six common air pollutants are subject to the Environmental Protection Agency's National Ambient Air Quality Standards (NAAQS) and are monitored throughout the US: carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), particulate matter (PM) and lead (Pb). In addition to these criteria air pollutants, EPA has identified 188 hazardous air pollutants (HAPs) which are known or suspected to cause cancer or other serious (e.g., reproductive) health effects. These HAPs include specific volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), dioxin as well as inorganic compounds such as arsenic. While EPA does not systematically monitor these compounds throughout the US, monitoring data for some of these air toxics are available in Atlanta. Specific air pollutants and classes of air pollutants are discussed below.

Carbon Monoxide (CO). Carbon monoxide is a gaseous pollutant and is emitted directly from anthropogenic sources, particularly from combustion processes such as the internal combustion engines of vehicles. In the US, road transport sources provide the majority of ambient carbon monoxide (Holman, 1999). While CO is considered a primary pollutant, there are secondary sources of CO; for example, CO is produced in the oxidation of volatile organic compounds (VOCs).

Sulfur Dioxide (SO_2). Sulfur dioxide is a primary gaseous pollutant released predominantly by power plants where coal and heavy fuel oil are burned (Holman, 1999). Relative to other pollutants, this gaseous pollutant is spatially heterogeneous, and concentrations can be affected by local plume touch-down events. Sulfate, a secondary particulate pollutant, is created through the oxidation of SO_2.

Nitrogen oxides (NOx). Nitric oxide (NO) and nitrogen dioxide (NO_2) are both primary and secondary gaseous pollutants. Most NOx is emitted from sources as NO and then oxidized to the NO_2 form; however atmospheric reactions can also convert NO_2 back to NO. Conversion back and forth between the two forms is driven by meteorologic conditions as well as atmospheric concentrations of other pollutants, namely ozone. Anthropogenic sources, primarily from mobile sources (gasoline and diesel vehicles), provide the majority of ambient NOx concentrations, though natural sources such as lightning, forest fires and bacterial soil activity also contribute. Ambient NOx also plays a role in ozone production and leads to the formation of secondary nitrate particles (Derwent, 1999; Holman, 1999). NOy, reactive odd nitrogen, includes NOx as well as the oxidation products of NOx, including nitric acid (HNO3), nitrous acid (HONO), nitrate particles (NO3), dinitrogen pentoxide (N2O5) and peroxyacetyl nitrate (PAN). Measured NOy provides an overall quantification of the total ambient oxidized nitrogen content (Seinfeld and Spyros, 1998).

Ozone (O_3). Ozone is a secondary pollutant generated by reactions between hydrocarbons, NOx and sunlight. Because of the importance of sunlight in driving these reactions, ozone exhibits a striking diurnal pattern with clear peaks in the afternoon hours. Ozone levels also shows dramatic seasonality, with the highest concentrations occurring in the warm summer months.

Particulate Matter (PM). Particulate air pollution, also referred to as aerosol, encompasses all airborne solid particles or liquid droplets which exist in a continuum of sizes and are composed of a wide array of organic and inorganic substances. The sources of PM are both natural and anthropogenic. Anthropogenic sources include power plants, incinerators, refineries, mobile sources (cars, trucks, buses); particles from natural sources, or bioaerosols, include pollen, spores, and particles from forest fires or volcanic eruptions. Particles can be either primary or secondary, although the smaller size fractions of PM contain a greater proportion of secondary particles (Pooley and Mille, 1999). The EPA systematically monitors and regulates PM according to size throughout the US; currently PM_{10}, particles less than 10 micrometers (μm) in diameter, and $PM_{2.5}$, particles less than 2.5 μm in diameter are monitored. PM_{10} constitutes the *inhalable* fraction of PM, particles which are small enough to enter the respiratory system. $PM_{2.5}$, are considered *respirable* because not only are these particles inhalable, but they are able to penetrate down to the actual air exchange surfaces of the lung (US Environmental Protection Agency, 2003). Particles between 2.5 and 10 μm in diameter constitute the coarse fraction of PM. Although ultrafine particles (particles less than 0.1 um) are not nationally monitored by EPA, interest in the potential health effects of this size fraction of PM is growing. However, these particles can be difficult to study as ultrafine particles can be extremely spatially heterogeneous with highly localized concentration spikes.

The complex chemical composition of PM exhibits tremendous variation, even within size fraction of PM. The major categories of *inorganic* $PM_{2.5}$ include secondary particles such as sulfates and nitrates, heavy metals and elemental carbon (EC). Nitrates and sulfates are formed from the oxidation of NO_2 and SO_2, respectively; other secondary particles include chlorides and other ammonium compounds (in addition to ammonium sulfate and ammonium nitrate). Heavy metals such as copper, iron, zinc, vanadium, platinum, magnesium and manganese exist in both water soluble and insoluble forms, and their presence in urban air pollution is generally a result of anthropogenic activities such as fossil fuel combustion. The oxidized form of metals is highly

insoluble. Concern about the health effects of metals stems from their crucial role in cellular metabolism and induction of oxidative stress through the production of free radicals (Ghio and Samet, 1999). Elemental, or black carbon, is released through incomplete fuel combustion; in particular diesel vehicles are a common source (US Environmental Protection Agency, 2003; Pooley and Mille, 1999). Because elemental carbon particles have a porous surface, they often absorb other particle species onto their surface (Pooley and Mille, 1999).

Airborne *organic* compounds can be classified into volatile, semi-volatile and non-volatile categories. Volatility, or the tendency for the compound to exist in gas rather than particle form, is dependent on a compound's molecular weight, the higher the molecular weight the more likely the compound will exist in particle form at ambient temperatures. Organic compounds (OC) found on particles include PAHs (discussed below), polychlorinated biphenyls and dioxins. Road transport constitutes the major source of organic compounds although other sources of combustion and incineration also contribute (Pooley and Mille, 1999).

Particulate matter is also made up of soil and mineral species which are lifted into the air by wind or on kicked up on roadways. In addition, biogenic species such as pollens, molds, plant fragments and insect parts are found in PM. These soil and biogenic species contribute primarily to the larger size fractions of PM (EPA, 2003; Pooley and Mille, 1999). The chemical composition of PM differs by region in the US, exhibiting some specific trends. For example, the eastern US tends to have more substantially sulfate and less nitrate than the western United States (NARSTO, 2003).

Polycyclic Aromatic Hydrocarbons. Polycyclic Aromatic Hydrocarbons (PAHs) are semivolatile, and exist in the atmosphere in both a vapor and particle form. In particle form, they contribute to the organic fraction of PM. Compounds with more aromatic rings, and consequently heavier molecular weight, are more likely to exist in the particle form. The health effects of PAHs likely differ between particle and vapor form. More than 90% of five and six ringed PAHs exist in the

particle form (Harrison, 1999). Whether or not a PAH compound exists in particle or vapor form is also influenced by humidity levels, as water vapor can compete for the absorptive surface areas of particles (Pooley and Mille, 1999). The primary origin of PAHs in the atmosphere is incomplete combustion of organic material, specifically from wood burning, coal combustion, aluminum production, and road transport sources (Holman, 1999). Like VOCs, many PAHs are known to have carcinogenic properties (Rushton and Cameron, 1999).

Volatile Organic Compounds. Volatile Organic Compounds (VOCs) exist in the air as vapor and can be further classified as alkanes, alkenes, aromatics, aldehydes, ketones, alcohols, acids, ethers or halogenated species (Rushton and Cameron, 1999). These compounds generally arise from anthropogenic sources such as traffic and industry, but certain species of VOCs are emitted from biogenic sources (vegetation). Atmospheric VOCs are a necessary precursor to the formation of ozone, but also have direct effects on human health in high enough doses. Many VOCs have been observed as genotoxic mutagens. It is unknown if current levels of ambient VOC concentrations are harmful to human health, as most studies investigating the health effects of organic compounds have been conducted in occupational settings where exposures are generally higher. Indoor sources of VOCs can contribute substantially to an individual's personal exposure. Exposure to benzene, an aromatic VOC, has been associated with certain types of cancer, blood disorders and at extremely high levels toxic effects on the central nervous system (Rushton and Cameron, 1999).

During the summer months when it is sunny and warm, photochemical activity by organic peroxy radicals drive the reactions of nitrogen oxides (NOx) which lead to ozone formation. These organic peroxy radicals are formed by the oxidation of VOCs by hydroxyl radicals (OH). Because both the hydroxyl radical (OH) and the NOx involved in ozone formation are recycled, the rate of ozone production is limited by the rate of photochemical oxidation of VOCs. This rate is governed by the particular structure of the VOC; thus, different VOCs vary in

their ability to drive the formation of ozone. This has served as a means to classify VOCs (Derwent, 1999; Rushton and Cameron, 1999).

CHAPTER 3: METHODS

Study population

The study population consists of all births between 1994 and 2004 among mothers who reside in the five-county metro Atlanta region at the time of delivery. Residence in these counties is determined by the maternal residential county recorded on the birth record. The year 1994 corresponds to the advent of maternal residence geocoding by the Georgia Division of Public Health. Evaluation of these outcomes in relation to particulate matter components, however, will be limited to the study period of 1998-2004, when these air data are available.

Birth outcome data

All recorded births and fetal deaths for five-county Atlanta have been obtained for 1994-2004 from the Office of health Research and Policy at the Georgia Division of Public Health. The 1994-2004 retrospective cohort will be constructed using these individual-level electronic databases of births. Covariates to be obtained from vital and fetal death records include maternal age, race, education, parity, tobacco use and frequency, alcohol use and frequency, prenatal care and visit frequency, marital status, medical risk factors, obstetric procedures, delivery method, abnormal conditions, labor complications and history of spontaneous abortion. The "medical risk factors" field on the birth record includes factors such as history of a preterm, low birth weight or stillborn baby, diabetes, hypertension and pre-eclampsia.

For the outcome of preterm delivery, we will consider all deliveries occurring after 20 weeks gestation. Only singleton live births without congenital birth defects whose delivery was not medically induced will be included in the cohort. Preterm delivery will be defined as birth at less than 37 weeks completed gestation.

Although ultrasonic examination is the preferred method to evaluate IUGR, these measures are not available on a population-wide basis. Therefore, we will define IUGR as birth

weight equal to or below the 10th percentile for gestational age, sex, race and parity. The most commonly used metric of SGA in the literature is birth weight in the bottom 10th percentile for gestational age and sex; however, race and parity also explain some of the natural variation in birth weight for a given gestational age. By incorporating some of the physiological variables which determine growth potential into the definition of SGA, we can better identify the infants who have experienced the pathology of IUGR (Gardosi, 1995; Gardosi et al., 1995; Kramer et al., 2001; Shiono et al., 1986; Zhang and Bowes, 1995). Percentiles of birth weight will be defined internally using the study population. Ideally a national standard of birth weight for gestational age would be used to facilitate outcome definition comparability across studies. Unfortunately, the only published national standard which incorporates race, sex and parity is limited to black and white race and gestational ages 25-42 weeks (Zhang and Bowes, 1995). We will also use a continuous measure of birth weight while controlling for gestational age to examine IUGR. Because congenital birth defects and multiple births strongly influence birth weight, only singleton births without congenital birth defects will be eligible for inclusion in the IUGR analyses.

For our secondary outcome of interest, we will consider birth weight without controlling for gestational age. Because an infant's birth weight is determined by both gestational age and fetal growth rate, a measure of crude birth weight combines the two outcomes into one robust measure of infant health. Much of the mortality and morbidity associated with prematurity and IUGR is attributable to low weight at birth (Wilcox and Skjaerven, 1992). Low birth weight will be defined as birth weight of less than 2500 grams, but we will also examine a continuous measure of birth weight.

Estimation of gestational age. An estimate of gestational age is required to examine both preterm delivery and IUGR outcomes in relation to air pollution. It should be noted that by obstetric convention, any estimate of gestational age includes the approximately 14 days before

fertilization. Vital records from the Georgia Division of Public Health provide and estimate of gestational age using one of three methods: the date of the last menstrual period (LMP), the clinical estimate of gestational age and an imputation of gestational age. Gestational age is calculated using the LMP date and the birth date, consistent with standard definitions, for approximately 98% of births. The clinical estimate of gestational age which is used in approximately 2% of births, is made by a physician at the time of birth. This estimate may be influenced by the weight and size of the baby, which would lead to SGA infants systematically misclassified as appropriately sized infants at a younger gestational age. Imputed gestational age (0.2% of births) is based on birth weight based algorithms at the Georgia Division of Public Health. If air pollution affects both gestational age and fetal growth, the use of birth weight to determine gestational age is problematic. Therefore we will limit the data to LMP-derived gestational age. The overwhelming majority of birth records from the Georgia Division of Public Health report a gestational age based on LMP date. The gestational age field on the birth records indicates which source of gestational age was used: LMP, clinician's estimate or imputation. We will be able to explore the use of other imputational strategies which are independent of birth weight for calculating a gestational age where the LMP month and year are complete (Taffel et al., 1982).

Data quality on vital records. The limitations of LMP-derived gestational age have been widely reported in the scientific literature; however, a more precise and reliable population-wide measure of gestational age is currently unavailable. Methods which would allow for prospective observation of gestational age such as first trimester ultrasound scanning or hCG urine measures would be impractical in a cohort of this size. According to the literature, errors in estimation of LMP can be attributed to post-conception bleeding, menstrual irregularities, late ovulation and poor recall (National Center for Health Statistics, 2004). Previous studies examining the quality of vital statistics data have shown that accuracy and missingness of LMP estimates can vary by

race and socioeconomic status (SES) (David, 1980; Taffel et al., 1982). Gestational age based on the LMP is most likely accurate when delivery is at or near term; post-term infants are more likely to have inaccurately reported LMP (Kramer et al., 1988; Mongelli and Gardosi, 1997; Savitz et al., 2002; Wegienka and Baird, 2005; Yang et al., 2002). We expect the quality of certain covariates on vital records to be poor. Although some birth record data such as birth weight and delivery method is generally considered reliable, tobacco, alcohol use and conditions which may affect risk of these birth outcomes such as diabetes and eclampsia are underreported (Buescher et al., 1993; Reichman and Hade, 2001; Northam and Knapp, 2006).

Because of these data quality issues, a temporal analytic strategy will be applied to the data to avoid potential biases created by spatial variability in the quality and completeness of vital record data. In addition, we will be examining birth weight without control for gestational age. Although examining birth weight unadjusted for gestational age will not separate the potentially independent etiologies determining length of gestation and fetal growth rate, birth weight is one of the most complete and unbiased aspects of the birth record (David, 1980). For the secondary spatial analyses which may be affected by these data quality issues, we will explore alternative ways to control for spatially varying factors. Socioeconomic status (SES) encompasses both individual- and community-level variables (Demarest et al., 1993). Accordingly, we will use individual- and community-level variables to characterize SES. Maternal education is one component of SES available from birth records; although this variable has measurement error, we believe that using maternal education is preferable to relying solely on a community-level variable. Krieger and colleagues recommend using the percentage of the population living below poverty in each census tract as the variable for community-level SES (Krieger et al., 2003a; Krieger et al., 2003b). Census tract poverty levels will be assigned using the geocoded maternal address at birth. We hope that confounding by SES can be minimized by using both individual level variables from the birth record and census tract poverty level. Ongoing efforts in a concurrent study of air pollution and birth the birth defects have quantified the accuracy of

geocodes on birth records in the five-county Atlanta area. Residential mobility patterns for a sample of infants in this cohort are also being examined. These validation studies will strengthen our understanding of the data quality and help us to quantify measurement error.

Analytic strategy

In light of all the issues surrounding the quality of vital records data, we have designed our study methodology to reduce vulnerability to these potential biases. For preterm delivery, IUGR and birth weight, our primary analytic strategy is purely temporal. We will be examining whether short-term changes in ambient pollution levels in Atlanta are associated with short-term changes in the rates of adverse birth outcomes; we will do this by comparing rates of the outcome between days instead of between individuals. In this time-series analysis, for a factor to operate as a confounder it must be related to the birth outcome and short-term (i.e., within season) changes in air pollution levels. Seasonal and longer term trends in the exposure, outcome and confounder will be controlled. For example, while SES is related to adverse pregnancy outcomes, it is not related to short term fluctuations in pollution levels and therefore cannot possibly be a confounder. Gradual change over time in SES levels in Atlanta will be controlled. Similar logic applies to race, smoking, diabetes, maternal age, prenatal care, occupational exposures, vitamin supplement use, obesity, etc. By extension, differential misclassification driven by these factors; for example, SES-related inaccuracies in LMP estimation, will not vary with short-term changes in pollution levels. Further discussion of the implications of gestational age misclassification is provided in the measurement error section of this proposal.

Causal relationships between birth outcomes

In the intrauterine growth restriction analyses of this dissertation, IUGR is defined as birth weight in the bottom 10% for gestational age, sex, race and parity. This outcome definition will necessarily misclassify normal, constitutionally small infants as IUGR, and may also misclassify some infants who are truly IUGR as normal, particularly in the preterm gestational age where a larger percentage of infants are thought to have experienced IUGR.(Bukowski et al., 2001; Zeitlin et al., 2000) However, using SGA as a proxy for true IUGR is advantageous in that it inherently controls for gestational age, so that preterm infants do not contribute a disproportional amount to the outcome of IUGR. Thus, if the etiology of prematurity is on the causal pathway to IUGR, this analysis will not detect an association between IUGR and air pollution because IUGR is defined within strata of gestational age. Any observed associations between IUGR (defined as SGA) and air pollution can be assumed to be independent of preterm birth. In contrast, the preterm birth analysis poses a more difficult problem, and motivates the use of sensitivity analyses to explore the possible influence of IUGR on the relationship between air pollution and preterm birth. Based on evidence demonstrating that preterm infants are more likely to have experienced fetal growth restriction, it is possible that an association between true IUGR, which cannot be directly measured in this study, and air pollution may induce a spurious association between preterm birth and air pollution. Sensitivity analyses for the preterm outcome, such as restriction to infants in the top 75% of birth weight for gestational age, may help to isolate the independent effect of air pollution on preterm birth by excluding the influence of most true IUGR infants.

Air Quality Data

Ambient pollution levels for this study will be obtained from three main sources: 1) the ARIES monitoring station, 2) the Georgia Tech $PM_{2.5}$ network, and 3) the state network of ambient air quality monitoring stations. Air quality data have been compiled for the period January 1994 through December 2004. A map with the locations of the current monitoring

stations is presented in Figure 1. In addition to the database of daily ambient pollutant concentrations, pollution will be characterized using the source apportionment conducted by our collaborators at Georgia Tech, described below, and with a near-roadway traffic impact assessment.

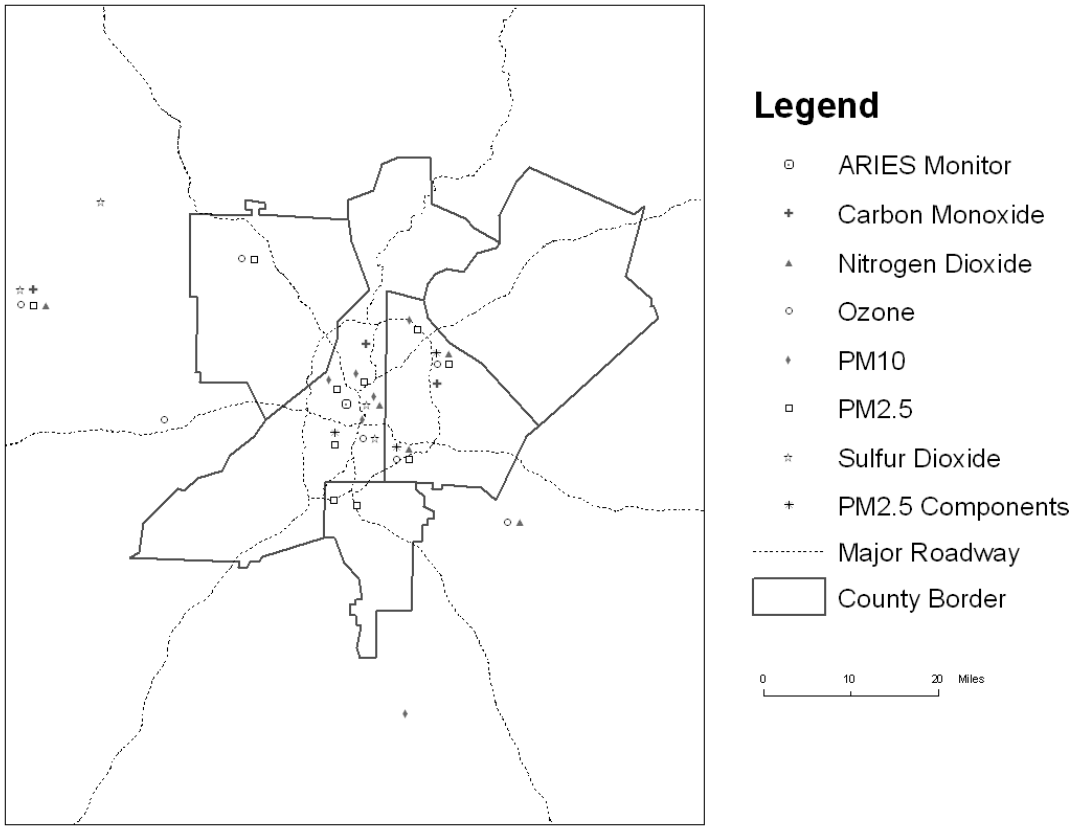


Figure 3.1: Locations of air monitoring stations in five-county Atlanta

Sources of air quality data

ARIES monitoring site. The Electric Power Research Institute (EPRI) launched an innovative air quality monitoring station located four kilometers northwest of downtown Atlanta on August 1, 1998, as part of the Aerosol Research Inhalation Epidemiology Study (ARIES). The ARIES superstation records numerous gaseous and particle pollutant measures, including total mass of PM_{10}, $PM_{2.5}$, and PM_{coarse} (PM with aerodynamic diameter between 2.5 and 10 microns), mass

measurements of the chemical components of $PM_{2.5}$, and particle counts of ultrafine PM (particles with aerodynamic diameter less than 1 micron). Several types of $PM_{2.5}$ measurement instruments are collocated at the ARIES site, methods include the federal reference method (FRM), particle composition monitor (PCM), and tapered element oscillating microbalance (TEOM). A dichotomous, filter-based sampler is used to measure daily PM_{coarse}. Measurements of components of $PM_{2.5}$ are made by PCM instruments designed by Atmospheric Research & Analysis, Inc. (ARA) and include sulfates, nitrates, organic carbon, elemental carbon, volatile organic compounds (VOCs) a water-soluble metal index (sum of soluble chromium, copper, iron, manganese, nickel, and vanadium) as well as individual water-soluble and water-insoluble metals concentrations. Continuous measurement of O_3, CO, SO_2, and NO_2 is conducted with standard instrumentation. Meteorological data, including daily temperature (mean, maximum, minimum), mean dew point temperature, relative humidity, barometric pressure, solar radiation flux, and pollen and mold counts are also recorded daily. In August 2000, the number of recorded analytes was slightly reduced; pollen and mold, ultrafine PM, and polar VOCs were dropped). A more complete description of the ARIES monitor is available elsewhere (Van Loy et al., 2000).

ARIES air quality data are collected and validated by researchers at ARA and EPRI using standard storage and handling techniques. Rigorous QA/QC procedures are in place, and tolerances for accuracy and consistency checks are within 5% and 10%, respectively. Our research team obtains air quality data from ARA and EPRI through a secure, password-protected internet website; however, much of these data are also publicly available. Additionally, close collaboration between the air quality scientists and the study investigators further enhances the quality of data from this monitoring effort. For the analytes that are measured at both ARIES and AQS, the correlations are generally extremely high. Furthermore, descriptive analyses have shown internal consistency in the data (Metzger et al., 2004; Peel et al., 2005; Van Loy et al., 2000).

Georgia Tech $PM_{2.5}$ network. Our Georgia Tech collaborators have been measuring $PM_{2.5}$ mass and composition at three Atlanta locations since March 1999, under the direction of Dr. Ted Russell. The three Georgia Tech (ASACA study) monitoring sites are: Fort McPherson Army Base, approximately 7 miles southwest of downtown, Tucker, approximately 12 miles northeast of downtown, and South DeKalb College, approximately 9 miles southeast of downtown. Particulate mass is measured continuously (resolved at one-minute intervals) using TEOM instruments, and PCM instruments provide integrated 24-hr composition data. The species collected on various filter media included ions (ammonium, sulfate, and nitrate), elemental and organic carbon, and metals (magnesium through lead) (Butler et al., 2003). Standard QA/QC procedures are included in the ASACA protocol.

State network of ambient air quality monitors. Several existing networks in the state of Georgia providing data on PM_{10} mass, $PM_{2.5}$ mass, O_3, CO, SO_2, NO_2, and pollen, as well as meteorology. Sources of data include EPA's Air Quality System (AQS), the Southeastern Consortium for Intensive Oxidant and Nitrogen measurements (SCION), the Clean Air Status and Trends Network (CASTNet), the Metro Atlanta Index (MAI) of the Georgia Department of Natural Resources, and the National Climatic Data Center (NCDC). Because they are part of the system that monitors compliance with federal air quality standards, the AQS monitors are subject to rigorous compliance guidelines, information requirements, information handling procedures, and standard methods of collecting, validating, and storing air pollution data. The monitor locations are selected according to prescribed criteria to maximize spatial representativeness and to avoid local sources that may influence the accurate measurement of the overall levels (Metzger et al., 2004; Peel et al., 2005).

Summary of air quality data. Table 3.1 provides a summary list of the pollutants of interest in this study, measurement method, sources of data, and time period for which data are available.

Table 3.1. The pollutants of interest, measurement method, sources of data, and the time period measurements are available.

Air quality variable	Measurement method (resolution)	Source of data	Dates data are available (Entire study = 1/1/94-12/31/04)
$PM_{2.5}$	FRM, PCM Teflon (discrete) TEOM (continuous) – collocated FRM (discrete) TEOM (continuous)	ARIES station State network (9 sites) GA Tech (3 sites)	8/1/98-12/31/04 5/1/1999 – 12/31/04 (6 are every 3rd day) 3/1/1999 – 12/31/04
PM_{coarse}	Dichotomous filter	ARIES station	8/1/98-12/31/04
PM_{10}	PM_{coarse} + $PM_{2.5}$ from ARIES (discrete) FRM (discrete)	ARIES station State network (7 sites)	8/1/98-12/31/04 Entire study (6 are every 6th day)
$PM_{2.5}$ sulfates	PCM nylon (discrete) PCM (discrete)	ARIES station GA Tech (3 sites)	8/1/98-12/31/04 3/1/1999 – 12/31/04
$PM_{2.5}$ organic matter	Denuded quartz filter (discrete) PCM (discrete)	ARIES station GA Tech (3 sites)	8/1/98-12/31/04 3/1/1999 – 12/31/04
$PM_{2.5}$ elemental carbon	Denuded quartz filter (discrete) PCM (discrete)	ARIES station GA Tech (3 sites)	8/1/98-12/31/04 3/1/1999 – 12/31/04
$PM_{2.5}$ water-soluble metals	PCM Teflon (discrete)	ARIES station	8/1/98-12/31/04
Volatile Organic Compounds (VOCs)	Evacuated 6-L passivated canisters	ARIES station	8/1/98-12/31/2004
Semi-volatile organic compounds (SVOCs) (eg. PAHs, polar compounds)	DRI Sequential Particle SVOC Sampler	ARIES station	8/1/1998 – 8/31/00
Ultrafine PM (<1 μm)	Univ. of Minnesota method (continuous)	ARIES station	8/1/1998 – 8/31/00
O_3	UV Absorption (continuous) Chemiluminescence (continuous)	ARIES station State network (13 sites)	8/1/98-12/31/04 Entire study (no winter data)
CO	Infrared analyzer (continuous) Infrared analyzer (continuous)	ARIES station State network (2 sites)	8/1/98-12/31/04 Entire study
SO_2	Fluorescence (continuous) Fluorescence (continuous)	ARIES station State network (3 sites)	8/1/98-12/31/04 Entire study
NO_2	Chemiluminescence (continuous) Chemiluminescence (continuous)	ARIES station State network (6 sites)	8/1/98-12/31/04 Entire study
Pollen	Rotorod sampler (discrete) Burkard sampler (discrete)	Atlanta Allergy Clinic ARIES station	Entire study 8/1/1998 – 8/31/00
Mold	Rotorod sampler (discrete) Burkard sampler (discrete)	Atlanta Allergy Clinic ARIES station	Entire study 8/1/1998 – 8/31/00
Temperature	Standard (continuous) Standard (continuous)	ARIES station State network (1 site)	8/1/98-12/31/04 Entire study
Dew point temperature	Standard (continuous) Standard (continuous)	ARIES station State network (1 site)	8/1/98-12/31/04 Entire study
Relative humidity	Standard (continuous) Standard (continuous)	ARIES station State network (1 site)	8/1/98-12/31/04 Entire study

Abbreviations – FRM: Federal Reference Method; PCM: particle composition monitor ; TEOM: tapered element oscillating microbalance; HEADS: Harvard-EPA annular denuder system

Source apportionment. An alternative approach to identifying the specific components of PM responsible for observed health effects is to explore associations between health outcomes and the sources contributing to pollutant levels (Laden et al., 2000; Manchester-Neesvig et al., 2003; Mar et al., 2000). Modeling health effects using emission sources of PM may be particularly constructive if the health effects of interest are due to a combination of pollutants or to components of PM which are not measured (i.e., it is not practical to measure every single $PM_{2.5}$ species). Quantifying the impact of specific pollution sources is particularly useful to regulators and has been highlighted as a research priority by the EPA (Gilman, 2004). In preliminary studies using source apportionment analyses; for example, mortality has been associated with combustion-related $PM_{2.5}$ (from motor vehicles, coal combustion and wood burning), but not soil-related $PM_{2.5}$, in both cohort (Laden et al., 2000) and time-series studies (Mar et al., 2000).

Collaborators at Georgia Tech are conducting source apportionment modeling of ambient particles in Atlanta from 1998 through 2002 for use in ongoing studies of air pollution and emergency department visits in Atlanta. They have employed two basic approaches to the source apportionment. The receptor based approach uses gas-to-particle ratios and particle composition data measured at monitoring stations in combination with knowledge about the physical characteristics of the pollutant emitted from sources to quantify the contribution to each day's air pollution by a source (Chemical Mass Balance, or CMB) (Marmur et al., 2005). In the emissions-based, or deterministic, approach (Community Multiscale Air Quality (CMAQ) model), meteorology and emission rates from specific sources are used to predict particle concentrations at different locations based on atmospheric advection, diffusion, chemical reactions and decomposition (Marmur et al., in press). Each approach has relative advantages and disadvantages. The receptor based approach (CMB) is able to resolve source contributions on a smaller temporal scale (e.g. at the day level) than the emissions-based approach (CMAQ). The emissions-based approach, however, is likely to provide a more spatially representative measure of source contributions for the Atlanta area.

Near-roadway traffic impact assessment. Because several studies indicate that primary mobile sources of air pollution may be particularly harmful, air pollution will also be characterized using a near-roadway traffic impact assessment (Grahame and Schlesinger, 2005). Using traffic data from the Georgia Department of Transportation and the Georgia Department of Natural Resources, traffic impacts will be assigned to each mother using the maternal residence geocode on the birth record. The traffic impact will be determined by residential proximity to roadways and the characteristics of those roadways such as vehicle miles traveled, speed, traffic zone type and other emissions factors. Using GIS software, we will construct a 550-foot radius around the geocoded location of each maternal residence. For each roadway intersecting this radius, the dispersion of motor vehicle exhaust from the roadway within the radius is estimated by a model similar to that developed by Pearson et al. (2000). This model assumes 1) 96% of motor vehicle exhaust pollutants disperse at 500 feet, 2) wind has little directional preference, and 3) pollutants are inert on the scale that dispersion is modeled. The model has the form:

$$Y = \sum_i \left(\frac{E_i}{0.4\sqrt{2\pi}} \right) \exp - \left[\frac{0.5(D_i / 500)^2}{(0.4)^2} \right]$$

where E_i is the estimated emissions from road i, D_i is the distance from the residence to road i and Y is the concentration enhancement from background levels in Atlanta due to proximity to road i. The near-roadway impact for the residence is calculated by summing the estimated annual emissions for each road intersecting the 550-foot radius. The assumption that 96% of motor vehicle exhaust is dispersed by 500 feet is based on previous studies which observed substantial dispersion of motor vehicle exhaust pollutant by this approximate distance from the roadway (English et al., 1999; Pearson et al., 2000; Wilhelm and Ritz, 2003). The uniform topography and lack of small scale directional wind preference in Atlanta justifies the omission of wind influence

in the model (Chang et al., 2005). This spatial analysis will allow for examination of spatially heterogeneous pollutant species contained in motor vehicle exhaust in relation to adverse birth outcomes.

Descriptive analyses

The temporal and spatial trends for air pollution, birth outcomes and possible confounders will be described with frequency tables, histograms, and plots with smoothers. A thorough descriptive analysis will aid our understanding of confounding by time trends and spatial heterogeneity. We will fully describe seasonal and longer term trends in prematurity and IUGR over the study period. We will look at the variation of these birth outcomes by factors such as maternal age, race, smoking and other individual-level covariates which may vary spatially. Furthermore, we will use alternative methods to account for temporal, seasonal, and spatial trends in both birth outcomes and air pollution, as described in the sensitivity analyses section appearing later in the text. Examples of preliminary spatial and temporal descriptive analyses are presented below (for illustration only – shown at less resolution than will be used in our analyses).

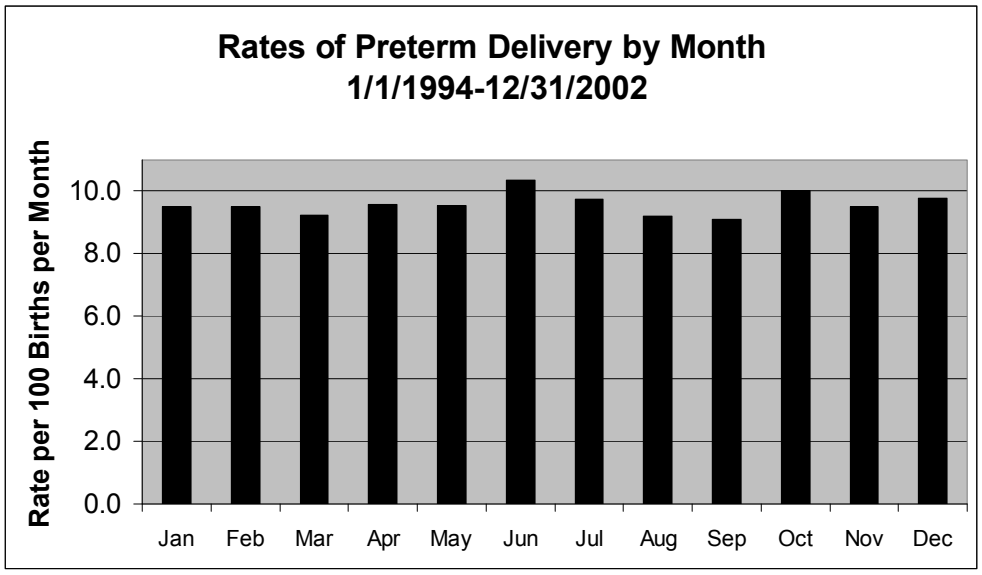


Figure 3.2: Temporal distribution of preterm delivery by month

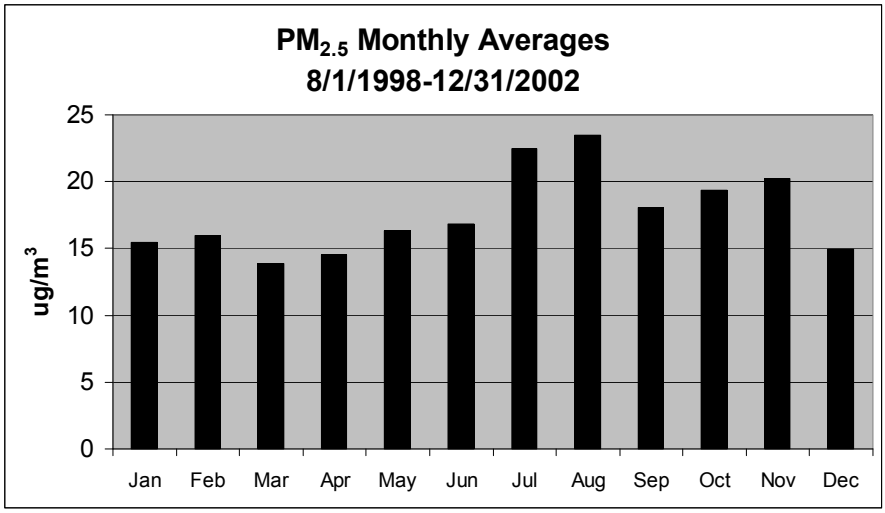


Figure 3.3: Temporal distribution of $PM_{2.5}$ by month

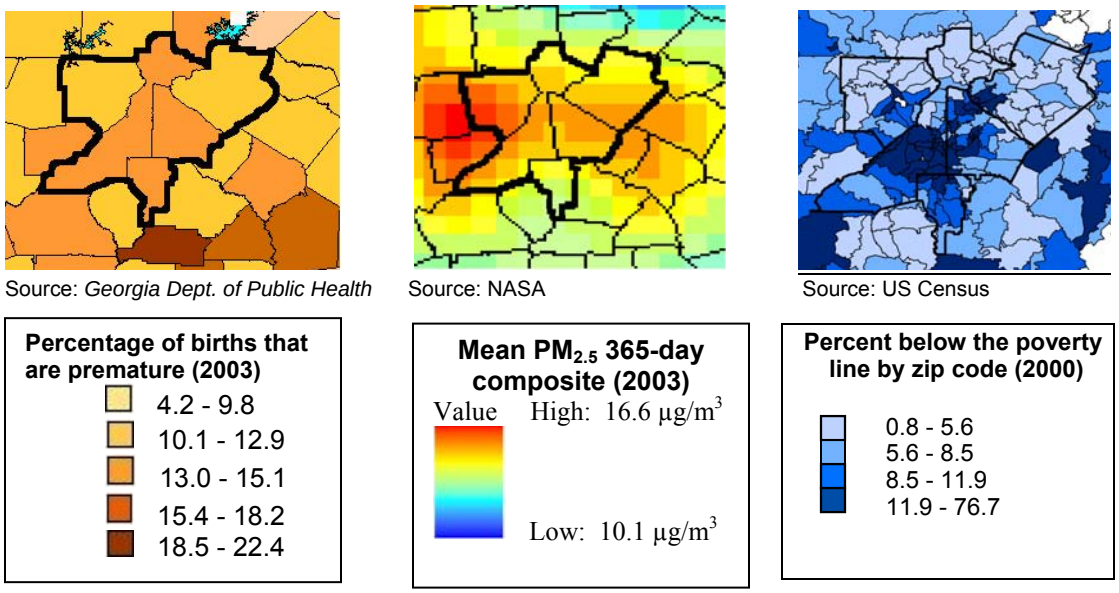
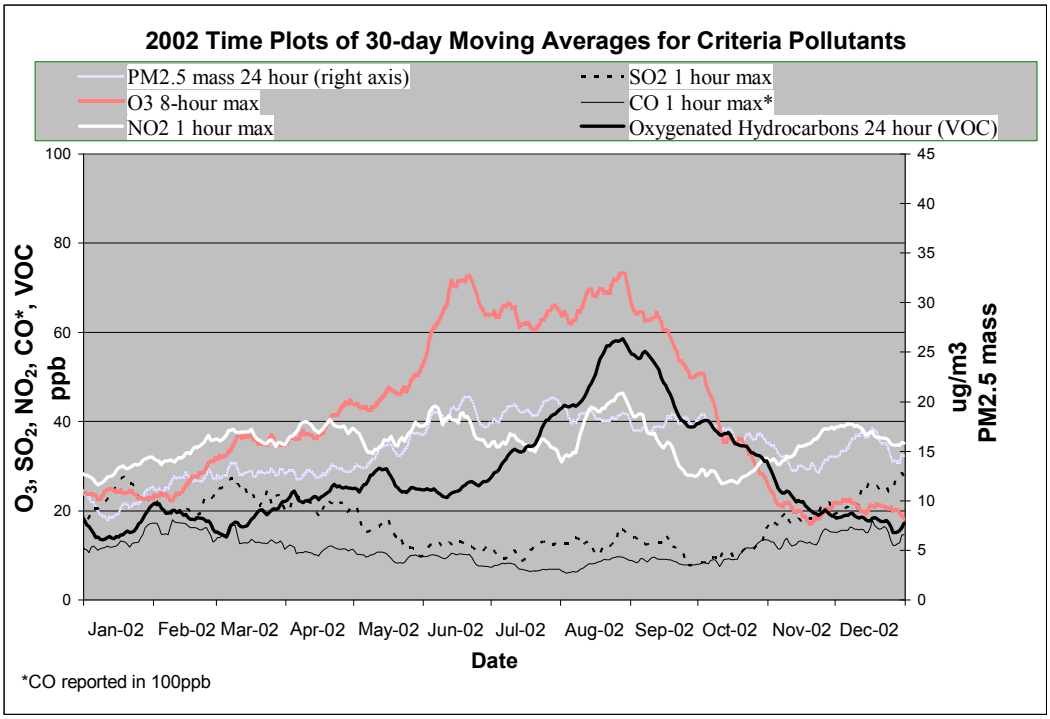


Figure 3.4: Spatial distribution of outcome, exposure and potential confounder in the five-county Atlanta area

Temporal variation and correlation of pollutants. The time plots and correlation table displayed in Figure 3.5 and Table 3.2 describe the temporal variation and correlation between the pollutants of interest. The time plots, which display 30-day moving averages for each pollutant throughout one year, show variation in the pollutants across time as well as sufficient divergence between pollutants.



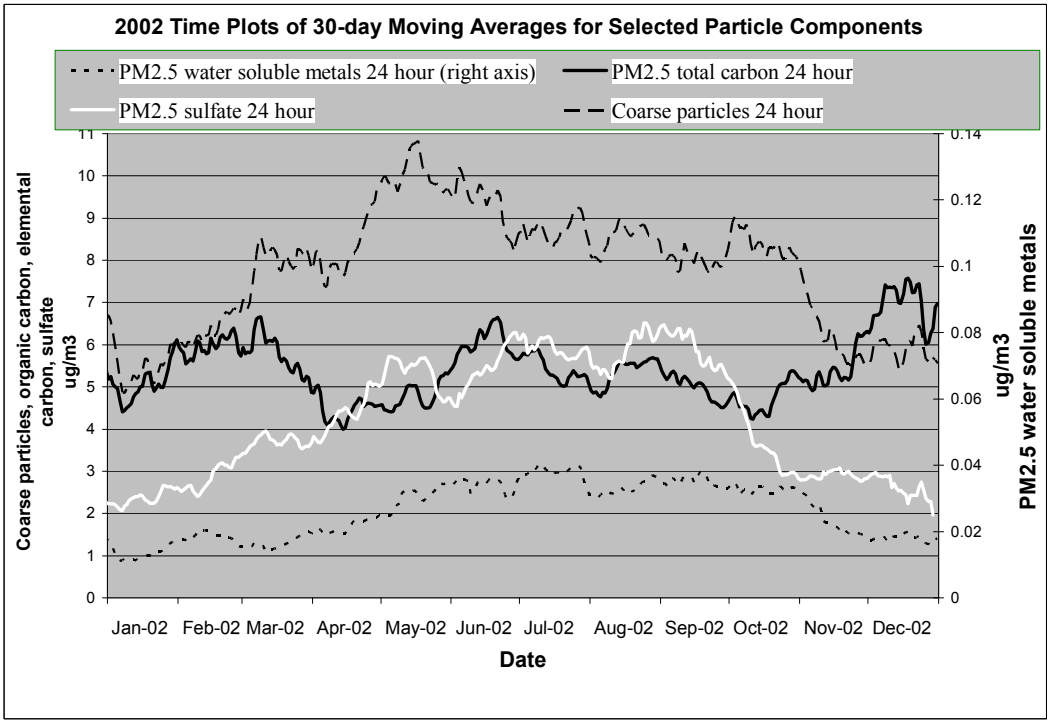


Figure 3.5: Time plots of 30-day moving average pollutant concentrations

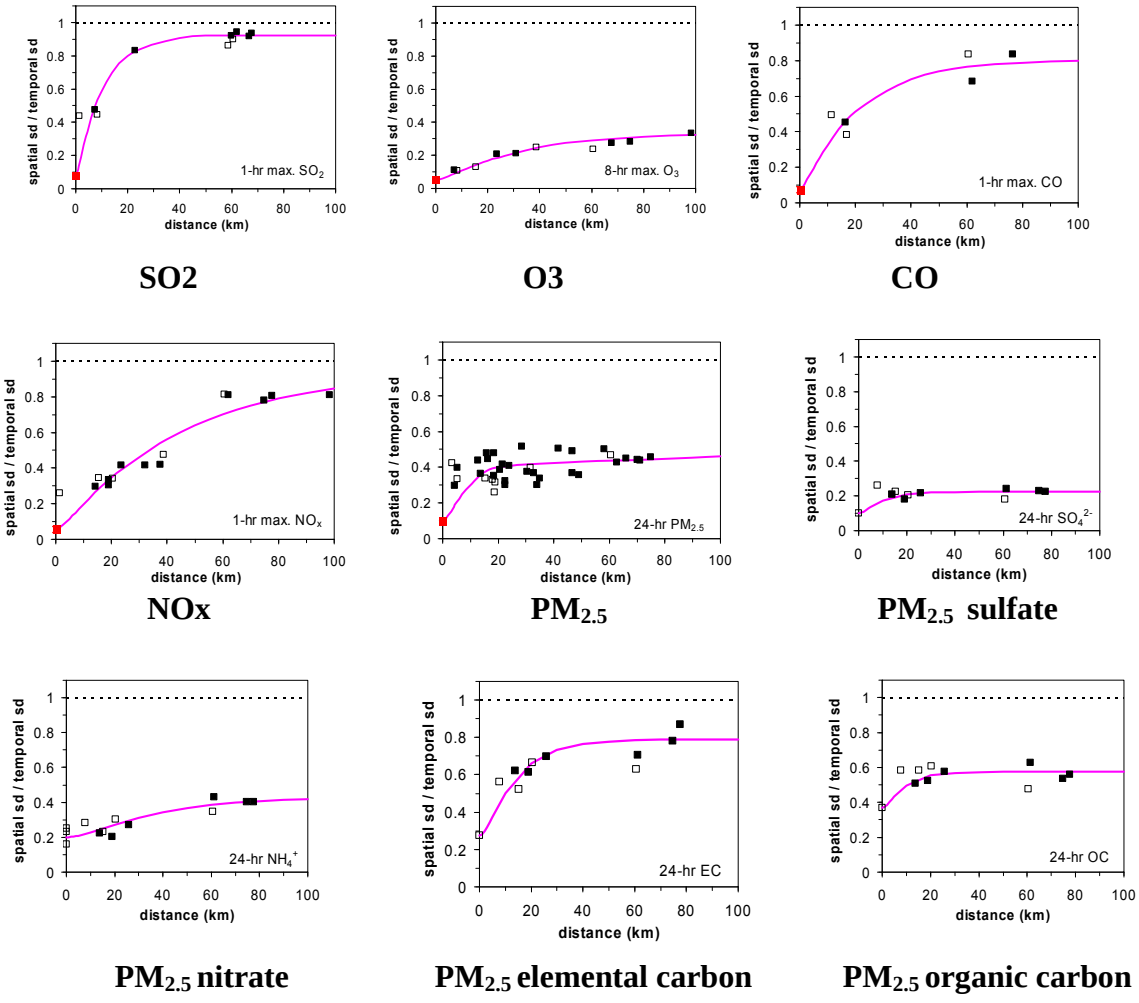
Table 3.2: Spearman Correlation Coefficients of daily pollutant measures, 1998-2004

	CO	NO_2	SO_2	O_3	PM_{10}	PM coarse	$PM_{2.5}$	$PM_{2.5}$ total carbon	$PM_{2.5}$ ws metals	$PM_{2.5}$ sulfate
CO	1									
NO_2	0.59	1								
SO_2	0.39	0.31	1							
O_3	0.09	0.45	-0.11	1						
PM_{10}	0.47	0.50	0.21	0.47	1					
PM_{coarse}	0.36	0.39	0.19	0.40	0.76	1				
$PM_{2.5}$	0.46	0.47	0.20	0.42	0.91	0.47	1			
$PM_{2.5}$ total carbon	0.66	0.55	0.25	0.25	0.72	0.51	0.71	1		
$PM_{2.5}$ ws metals	0.36	0.39	0.07	0.48	0.70	0.50	0.69	0.52	1	
$PM_{2.5}$ sulfate	0.12	0.36	0.03	0.61	0.68	0.32	0.76	0.34	0.65	1
Oxygenated hydrocarbon	0.24	0.27	0.04	0.37	0.46	0.37	0.43	0.37	0.41	0.41

Spatial heterogeneity of pollutants. In all of our analyses we will consider the spatial representativeness of each pollutant on a case by case basis. Our collaborators at Georgia Tech have characterized the spatial variability of a wide array of ambient air pollutants in the Atlanta area using tools such as wind rose plots and semivariograms, examples of which are displayed below. These assessments of measurement error due to spatial variability in Atlanta have informed other ongoing investigations of ambient air pollution and health effects in Atlanta. A recent publication specifically describes the spatial representativeness of the monitored pollutants in Atlanta, including PM components {Wade, 2006 #275}. Spatial representativeness differs between pollutants, with primary pollutants showing more spatial heterogeneity than secondary pollutants. The semivariograms presented below show the ratio of spatial variability relative to temporal variability at increasing distances between monitors for each pollutant. A value of 1.0 on the y-axis indicates that exposure uncertainty due to spatial variability equals the temporal variability for that pollutant. This information will be used in subanalyses in which the study area is adjusted to account for spatial variability of the pollutant under consideration, in analyses

where residence is assigned a weighted average of data from nearby monitors, and in the measurement error assessment, described below.

Figure 3.6: **Normalized semivariograms for ambient air pollutant measures in Atlanta, 1999-2002. Hollow points include the Jefferson St. ARIES station.**



Linking exposure and outcome

The assignment of exposure varies by analytic strategy (temporal or spatial) and the birth outcome of interest. For example, in the temporal analysis of preterm delivery, the counts of preterm births will be aggregated by day over the study period. Each day will be assigned a pollution value representing the average Atlanta pollution level over the past six weeks prior to

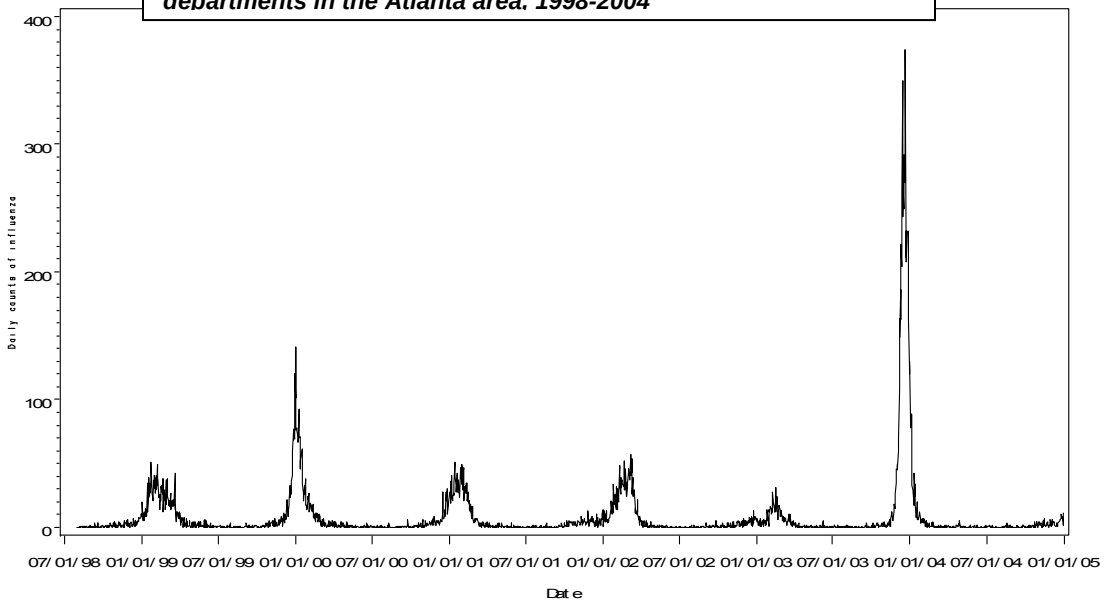
that day. This pollutant metric will be calculated as an average of measurements from multiple stations. For pollutants and pollutant constituents measured only at the ARIES site, the pollutant value from this central monitor will be used. The analysis will contrast the pollution metric in relation to rates of preterm birth across days. In the secondary individual-level analysis of preterm birth, exposure will be assigned using birth date and geocodes from the birth record to identify the closest ambient air pollution monitor (or weighted average of multiple monitors) to the maternal residence.

Assessment of potential temporal confounders

While the time-series approach precludes confounding by individual-level risk factors which are unrelated to time, temporal confounders must be controlled. Regression spines with seasonal knots are designed to account for unmeasured time varying confounding on a seasonal or longer time scale. However, any risk factor which exhibits within-season temporal variability in the population can potentially confound the relationship between ambient air pollution levels and adverse birth outcomes and therefore will require explicit control in the model. These factors include short-term temporal variation in infectious disease, airborne allergens, temperature, meteorology and diet. For example, there is evidence that preterm delivery is associated with various types of infection (Elovitz and Mrinalini, 2004; Hagberg et al., 2005; Leitich, 2005; Steer, 2005). Although we cannot ascertain subclinical infection, which would require a more resource intensive prospective design, our ongoing emergency department study uniquely positions us to assess the effect of several clinically manifested infectious diseases; we have comprehensive data from Atlanta emergency departments over the study period and can incorporate spikes in upper respiratory infections, pneumonia, gastrointestinal infections and influenza epidemics into our models. A sample time plot from our emergency department visit study showing temporal spikes in influenza is displayed in Figure 3.7; the spikes occur within season, and explicit control for

influenza peaks in temporal models may be appropriate. In addition to infectious diseases we will assess short term temporal changes in airborne allergens in the Atlanta area. The Atlanta Allergy Clinic maintains a record of daily pollen and mold allergen levels in Atlanta. Thirty-two pollen and 25 mold species are monitored daily and are available for the length of the study. This airborne biogenic material may be relevant to inflammatory hypotheses of the etiology of preterm birth. Recent animal experimentation data showing antigen-induced preterm labor in sensitized guinea pigs lends biological plausibility to the hypothesis (Bytautiene et al., 2004). Within-season temperature spikes and dips will also be assessed for confounding. While these temporally varying factors are not well established risk factors for preterm birth or IUGR, they are plausible risk factors, and the assessment of these factors as potential confounders may help to refine other hypotheses regarding the etiology of these adverse birth outcomes.

Figure 3.7. Daily influenza counts from all emergency departments in the Atlanta area, 1998-2004



Statistical Models for Preterm Delivery

In order to reduce the likelihood of spurious findings due to multiple comparisons we have taken a hierarchical approach and will focus our analyses on *a priori* gestational windows of

exposure motivated by previous reports: the 6 weeks prior to delivery and the last week before delivery (Ritz et al., 2000; Sagiv et al., 2005). In a secondary analysis, we will also examine exposures in the first month of gestation in relation to preterm birth. In our primary analytical approach we will employ a Poisson GEE model on aggregated count outcomes to assess the temporal relationship between preterm delivery and ambient air quality. The basic time-series model has the form:

$$\log(E(Y_t)) = \text{offset} + \alpha + \beta * \text{pollutant}_t + \delta * (\text{temporally varying covariates}_t)$$

Y_t represents the number of preterm births on day *t*. The offset is the log of the number of pregnancies at risk for preterm birth on day t; prior to week 20 and after 37 weeks gestation a pregnancy is not at risk for preterm delivery. The pollutant concentration represents our two primary gestational windows of interest: the average concentration in the Atlanta area over the previous six weeks, or the average concentration over the past seven days. Temporally varying covariates may include regression splines for the control of time trend, seasonality, meteorologic conditions, influenza, and airborne allergens (as discussed above). These covariates are either known or plausible correlates of preterm delivery and air pollution. Indicator variables for day of week and holiday will also be included. An autoregressive correlation structure will account for possible autocorrelation in the residuals.

The outcome can be defined broadly or finely with regard to gestational age at birth, and because of our large study population we have the statistical power to stratify on gestational age. Preterm deliveries at 34 weeks on a given day can be compared to all gestations at 34 weeks on that day, thus allowing for a comparison of exposure over the same gestational window in all pregnancies. It is plausible that the relationship between the rate of preterm delivery and air pollution exhibits heterogeneity across different gestational ages; e.g., a greater pollution insult may be required to trigger a preterm delivery earlier in gestation than later in gestation. Our

stratified approach will allow us to assess the possibility of effect modification across different gestational ages. If no heterogeneity is indicated, counts will be pooled across gestational ages to gain precision in the model.

This time-series approach aggregates the data into daily counts of preterm delivery and assigns a single pollutant value for Atlanta to each daily count. The pollution value assigned to each day represents the pollution over the past six weeks (or one week) and will be a weighted average of the measures from all monitors in the Atlanta area during that time period. A key advantage of using a time-series approach is that individual-level factors, such as vitamin supplement use, race and occupational exposures, cannot act as confounders unless they are related to short-term (within season) changes in air pollution, which is generally unlikely. We have designated the time-series approach as our primary analysis in order to minimize vulnerability to these individual-level confounders. For maternal smoking to be a confounder, for instance, mothers would have to alter their smoking habits over the course of their pregnancy in a way that is correlated with daily fluctuations in air pollution levels. Long term population trends in smoking prevalence will be accounted for by the regression splines. Temporal confounders operating within season, however, will be assessed as described above.

As a secondary analysis, logistic GEE models will be used in a discrete survival analysis of the cohort of pregnancies at risk for preterm birth. This individual-level logistic model will allow for finer spatial resolution of ambient concentrations. Using maternal residence geocodes, we can assign pollutant levels using the most relevant monitor or monitors. Pollution assignment will be a weighted average of all appropriate pollutant monitors, with the closest monitors contributing the most weight. The determination of appropriate monitors will be based on the spatial variability of each pollutant as described earlier in this proposal. The survival analysis will include all individuals, beginning at gestational week 20 and followed (historically) until birth or week 37 when they are censored (whichever comes first). The basic spatio-temporal model has the following form:

$\text{logit}(E(Y_{it})) = \alpha + \beta^* \text{pollutant}_{it} + \delta^*(\text{temporally varying covariates}_{it}) + \eta^*(\text{spatially varying covariates}_{it})$

Y_{it} is the dichotomous outcome indicating whether or not the i^{th} subject was born on day t of gestation, conditional on having reached day t of gestation. The pollutant term refers to the average pollution over the previous six weeks (or one week) from day t. In addition to the temporally varying covariates discussed in the previous model, the logistic models will control for spatially varying covariates, including maternal characteristics such as maternal education, maternal age, parity, pregnancy complications and previous preterm delivery. Because each subject's gestation contributes multiple observations (each observation corresponds to one day of follow-up over a subject's risk period), the model will become computationally intensive. If this affects our model convergence, we will randomly sample controls from the pool of pregnancies at risk on a given day of gestation.

The spatio-temporal analysis will include a near-roadway impact characterization of pollution in order to explore the relationship between preterm delivery and residential proximity to roadways. The calculation of this value for each mother is described previously. For this analysis, the pollutant metric representing average pollutant level over the previous six (or one) weeks is replaced by the near-roadway impact (NRI):

$\text{logit}(E(Y_{it}))= \alpha + \beta^*\text{NRI} + \delta^*(\text{temporally varying covariates}_{it}) + \eta^*(\text{spatially varying covariates}_{it})$

Like other spatial approaches, this model will be vulnerable to confounding by individual-level factors if the prevalence of an unmeasured risk factor for preterm delivery is associated with living near roadways. Relevant individual-level covariates such as maternal education, age and smoking status will be controlled to the fullest extent possible. This analysis is motivated by

evidence that pollution derived specifically from mobile sources may be particularly harmful (Grahame and Schlesinger, 2005).

Our *a priori* hypothesis is levels of ambient particulate matter averaged during the six weeks prior to delivery, and the seven days prior to delivery, are associated with the rate of preterm delivery. In primary analyses we will consider PM_{10}, $PM_{2.5}$, carbon monoxide (CO), and sulfur dioxide (SO_2). Secondary analyses will examine components of $PM_{2.5}$ (total carbon, sulfate, water soluble metals), sources of PM, ozone (O_3) and nitrogen dioxide (NO_2). Ambient levels of these pollutants during the first month of pregnancy, a secondary gestational window of interest, will also be assessed. The examination of preterm delivery in relation to specific sources of air pollution will be carried out using the results of the source apportionment analyses conducted by collaborators at Georgia Tech.

The relationship between air pollution levels and adverse birth outcomes may not be linear. In all analyses, we will explore the shape of the dose-response curve. We will assess whether the use of particular transformations (e.g., log) will accommodate the use of a linear pollution term in the model. We will test for nonlinearity both visually and statistically, comparing models containing linear pollutant terms to models with splines fit to pollution variables. Additionally, we will conduct analyses in which pollution quantile categories will be represented in the model by indicator variables.

Statistical Models for IUGR

In order to separate the biological processes of intrauterine growth rate and length of gestation, we address the issue of fetal growth after adjusting for gestational age using two characterizations of birth weight. The use of a continuous as well as a dichotomous measure of birth weight allows for the examination of the entire birth weight distribution as well as the lower tail of the distribution. For the analyses of both small for gestational age and continuous birth

weight, our *a priori* gestational window of interest is the third trimester. The first month of gestation will be examined as a secondary window of interest.

Like the preterm analysis, our primary analytical approach will be a temporal analysis for both gestational windows. However, a limitation of a purely temporal approach for the third trimester exposure window is that averaging pollution levels over a trimester will decrease the variability of exposure after seasonal effects are controlled for using splines. In addition to the primary temporal approach, we will conduct an individual-level spatio-temporal analysis as a secondary analysis; with this approach we will gain a more efficient analysis with greater exposure variability. The caveat to this approach, and all individual-level spatio-temporal analyses, is that individual-level covariates must be well controlled.

Models for small for gestational age. The outcome is a dichotomous variable indicating SGA as the lowest ten percent of birth weight within strata of gender, race, parity and gestational age. Small for gestational age will be determined using internally defined birth weight distributions. The basic logistic GEE model, which can be used for both temporal and spatio-temporal analyses, has the form:

$$\text{logit}(E(Y_t)) = \alpha + \beta*\text{pollutant}_t + \delta*(\text{temporally varying covariates}_t) + \eta*(\text{spatially varying covariates}_t)$$

Y_t represents the dichotomous SGA outcome on the subject's birth date *t*. The definition of the outcome inherently controls for gender, race, parity and gestational age. The pollutant term represents the average pollution from the beginning of the subject's third trimester (gestational day 196) to day *t*. Because some infants have shorter gestations than others, the length of the third trimester, and thus the exposure period of interest, will vary. Under the assumption that the exposure of interest is the average level of air pollution during the third trimester, as opposed to maximum level for example, different lengths of pollution averaging should not create a bias

(after control for long term trends). However, the asymmetry in the averaging time over the third trimester motivates the use of sensitivity analyses to explore this issue further. These sensitivity analyses will include a restriction to full term infants so that only infants with a full third trimester are included in the analyses. Furthermore, we have the statistical power to stratify on gestational age, so that comparisons for this analysis can be made between infants with the same sized averaging windows. Temporal and spatial control is similar to that described for the previous models including control for individual maternal characteristics such as previous delivery of a SGA infant. This logistic model contrasts with the model described for preterm birth in that there is one observation per subject (on birth date); for preterm birth the discrete survival models use multiple observations per subject until birth or censorship at 37 weeks gestation. The shape of the dose-response curve will be fully explored, as described for preterm birth.

Models for birth weight. Linear GEE models for a continuous measure of birth weight, stratified by gestational age at birth (by week), will be employed. The basic model, which can be used for both temporal and spatio-temporal analyses, has the form:

$$E(Y_{ts}) = \alpha + \beta * \text{pollutant}_{ts} + \delta * (\text{temporally varying covariates}_{ts}) + \eta * (\text{spatially varying covariates}_{ts})$$

Y_{ts} represents the birth weight on the subject's birth date *t*, within gestational age stratum *s*. The pollutant term represents the average pollution from the beginning the subject's third trimester to day *t*. Temporal and spatial control is similar to that described for the previous models. In an alternative approach to controlling for gestational age, we will utilize indicator variables representing week of gestation which will provide fuller use of the data at the expense of more reliance on the assumptions of the model. Effect modification between air pollution and gestational age on birth weight will also be evaluated using this model.

We hypothesize that the average level of ambient pollution during the third trimester is related to the outcome. PM components and sources as well as other gaseous pollutants are of secondary interest. In addition, the first month of pregnancy will be examined as a secondary gestational window of interest.

Primary analyses will be focused on PM_{10}, $PM_{2.5}$, and CO. Secondary analyses will utilize other gaseous pollutant, and PM component data in the evaluation of IUGR. A near-roadway impact assessment will also be conducted for the IUGR outcome analogous to that described for preterm delivery.

Statistical Models for Crude Birth Weight

We will model the relationship between air pollution and birth weight, unadjusted for gestational age. Because birth weight is determined by both length of gestation and fetal growth rate, examining birth weight unadjusted for gestational age will not separate out these two gestational processes. Nevertheless examining this outcome will provide a global metric of fetal health without misclassification of outcome introduced by measurement of gestational age. If air pollution is associated with both prematurity and IUGR, we should also observe an association with crude birth weight. Analyses of this outcome will be analogous to the analyses for IUGR. Primary analyses will focus on PM_{10}, $PM_{2.5}$ and CO, pollutants of primary interest for both the preterm delivery and IUGR outcomes. Other gaseous pollutants, PM components and PM sources will also be evaluated in secondary analyses. In sensitivity analyses for this outcome, we will examine exposure in the last ten weeks of gestation. While this will include part of the second trimester for preterm infants, this exposure metric will eliminate the misclassification of exposure introduced by gestational age estimation and will avoid the issue of different sized gestational windows for preterm and term infants.

Multiple Comparisons

With multiple pollutants, outcomes and gestational windows of interest, it is likely that spurious associations will emerge by chance (Type 1 error). Unfortunately, the literature is heterogeneous with respect to the pollutants of interest and critical gestational time periods for these outcomes. We have carefully examined the literature and prioritized gestational windows for which we believe the evidence is most compelling. However, a hierarchical approach does not preclude full exploration of the data. In the case that we have misspecified the gestational period of interest, secondary and exploratory analyses may help inform future studies in this emerging area of air pollution research. We have taken a similar approach to the air pollution variables by selecting a small subset out of the hundreds of available air quality measures for this analysis. We have prioritized particles and CO (and SO_2 for preterm analyses) as being of primary interest, with other gaseous pollutants, PM components and PM sources examined in secondary analyses. As an additional approach, we explore the use of empirical Bayesian analyses to provide an overall structure to potentially disparate analytic results. Greenland and Robins (1991) and Greenland and Poole (1994) argue that, under certain assumptions, the use of empirical Bayesian methods can be a practical approach to addressing the problem of multiple comparisons. When a large number of comparisons are made, empirical Bayes adjustments may help to identify the most promising leads for future studies (Steenland et al., 2000). This approach is useful for examination of PM components and sources, for which there is little *a priori* knowledge available to inform our judgment about each individual comparison. In this empirical Bayesian approach, effect estimates for the different sources and components of PM over the different gestational time windows will regress to the overall mean; the degree of shrinkage toward the mean is a function of each estimate's standard error**.** Each of the individual effect estimates is then re-interpreted; this reduces the occurrence of extreme effect estimates due to chance fluctuations (Greenland and Poole, 1994; Greenland and Robins, 1991).

Sensitivity analyses

We will conduct sensitivity analyses to assess the sensitivity of results to the modeling strategies employed and to potential confounding due to temporal or spatial trends in the birth outcomes and air pollution. Because air pollution varies temporally and spatially, tight control of both temporal and spatial variables can reduce variability to the extent that the effect of air pollution cannot be evaluated. On the other hand, tight control for geographic region reduces potential confounding by geographic area, and tight control for temporal trends reduces the possibility of confounding by temporal factors. In one set of sensitivity analyses for both temporal and spatio-temporal models, splines with additional knots will be added to the model to more fully account for seasonal and temporal trends. In the spatio-temporal models, another set of sensitivity analyses will control more tightly for geographic variation, allowing temporal variation to drive the results.

We will also explore alternative lag structures to our uniform moving average of exposure over the gestational windows of interest. By using a polynomial function of the lagged exposure parameters (i.e., distributed lag) we may be able to more specifically identify weeks or days during gestation when the fetus is particularly susceptible to air pollution. Additionally, we will assess whether statistically controlling for additional risk factors available from vital records (including alcohol consumption and obesity correlates such as hypertension and eclampsia) affects the results obtained from spatio-temporal models; the quality of these data will be considered in interpretation of these results. Small for gestational age in this study is defined using internal distributions of birth weights, defined within strata of race, sex, parity and gestational age. We will explore the sensitivity of the results to the use of an alternative 10% threshold from an available national standard; this analysis will be limited to black and white infants between 25-42 gestational weeks due to limitations of the national standard (Zhang and Bowes, 1995). We will also attempt to separate any effect of IUGR from the association between air pollution and preterm birth by restricting preterm analyses to infants with birth weights in the

top 75% for gestational age. As described in the IUGR and birth weight analysis sections, we will explore the issue of different averaging window length over the third trimester by restricting analysis to full term infants as well as conducting gestational age stratified analyses. For the outcome of crude birth weight (birth weight unadjusted for gestational age), we will perform sensitivity analyses using pollution levels in the 10 weeks before birth. While these 10 weeks will incorporate part of the second trimester for preterm infants, this exposure metric does not rely on a measure of gestational age to determine the exposure window and will again avoid the problem of different lengths of third trimester averaging windows. Finally, we will conduct spatial subanalyses in both the temporal and spatio-temporal models, restricting inclusion to mothers living within close proximity to a monitor. Our final interpretation and conclusions will reflect and incorporate the results of these sensitivity analyses and weigh their relative strengths and weaknesses.

Measurement error

Vital Records. The use of vital records data will unavoidably lead to some misclassification of exposure and outcome. While use of LMP on the birth record to estimate gestational age will introduce misclassification of exposure, this is not expected to create a substantial bias. For intrauterine growth retardation and birth weight, the primary exposure window is a three month period, and thus small inaccuracies in gestational age are unlikely to affect the exposure assignment. For preterm delivery, the primary exposure window of interest is based on birth date (6 weeks or 1 week prior to birth) and birth date is recorded accurately on the birth record. In the stratification by gestational age in the preterm analysis, although there will be gestational age misclassification, we feel our approach is a substantial improvement over previous studies which did not make any attempt to compare pollution levels for preterm infants with pollution levels for infants in the same gestational stage. Derivation of gestational age from the LMP will also lead to misclassification of *outcome* in the preterm analyses. Some infants will be incorrectly classified

as either preterm or full-term due to inaccurate determination of gestational age and some infants will be incorrectly classified as SGA. In our preferred temporal analysis, while this will create noise in the outcome, we will be comparing the rate of the outcome across days; the degree of misclassification is expected to be similar across days, particularly in the short term.

In our spatial analyses, there will be misclassification of exposure assignment due to residential mobility during pregnancy (Khoury et al., 1988). However, maternal residence is recorded on the birth record at the time of birth, and three of our four exposure windows (the last week before birth, the last six weeks before birth, and the last trimester) are toward the end of pregnancy. Our secondary gestational window of interest, the first month of pregnancy, overlaps the gestational window of interest for the concurrent birth defects study, and results of a residential mobility assessment currently underway at the CDC will be incorporated into spatial analyses for all birth outcomes. Notably, misclassification due to residential mobility in the temporal analyses would only occur if a mother moves from outside the five-county Atlanta area to inside this area between the exposure window and delivery. The degree of misclassification due to uncertainty in the coordinates of the geocoded maternal address is also being assessed. Of the 665 maternal addresses validated to date, the median location error for the geocodes is 91 meters. The distribution of this source of measurement error (the distance between the geocoded coordinate and the residence) will be formally incorporated into our measurement error assessment. Although we anticipate that the impact of these sources of misclassification is likely to be relatively small and non-differential (biasing results towards the null), we nevertheless believe it is prudent to assess these biases.

Misclassification of certain covariate data, however, may be differential with respect to exposure and outcome and could therefore bias the results in either direction. For the temporal analyses of preterm delivery, the misclassification of individual-level covariate data on the birth records will not be an issue. However, in the spatial analyses, the uncertainty for important covariates will be explored and incorporated into our conclusions. The measurement error

associated with the use of vital statistics data highlights inherent liabilities of the study design; alternative designs which would allow direct observation of gestational age and substantiated personal data such as residential history during pregnancy, occupational exposures and weight gain during pregnancy would be substantially more resource intensive and are not justifiable given the current state of knowledge.

Ambient Air Data. When ambient pollution levels are used to characterize air pollution in an epidemiologic investigation, there are several sources of exposure measurement error. Zeger et al. (2000) and Dominici et al. (2000) have conceptualized exposure measurement error in time-series studies as the sum of three components: 1) the difference between individual-level personal exposure and average personal exposure, 2) the difference between average personal exposure and the true ambient pollutant level, and 3) the difference between the true and measured ambient pollutant level (Dominici et al., 2000; Zeger et al., 2000). Because it is ambient air pollution which is regulated, a primary objective of our study is to describe the relationship between adverse birth outcomes and *ambient* levels of air pollution. Therefore we are most concerned with the third type of error: the difference between measured and true ambient level of pollution. Instrument error, local sources of pollution near monitors and spatial heterogeneity all contribute to this error. Zeger et al. (2000), argue that this source of error is largely of the Berkson type, which would not contribute bias to the regression coefficients unless the measured pollution level is a biased estimate of the true spatially averaged ambient level. Spatial heterogeneity of pollution levels is being assessed and quantified in ongoing work with our colleagues at Georgia Tech using the multiple sources of air pollution monitoring data in Atlanta. At present, there are 8 sites for PM_{10}, 13 sites for $PM_{2.5}$, 4 sites for SO_2, 14 monitoring sites for O_3, 7 sites for NO_2, 3 sites for CO, and 4 sites for $PM_{2.5}$ sulfates, nitrates, organic carbon, and elemental carbon. For many of the pollutants, we also have information on instrument error to incorporate into the measurement error estimate. As a secondary objective, we will consider the error introduced by

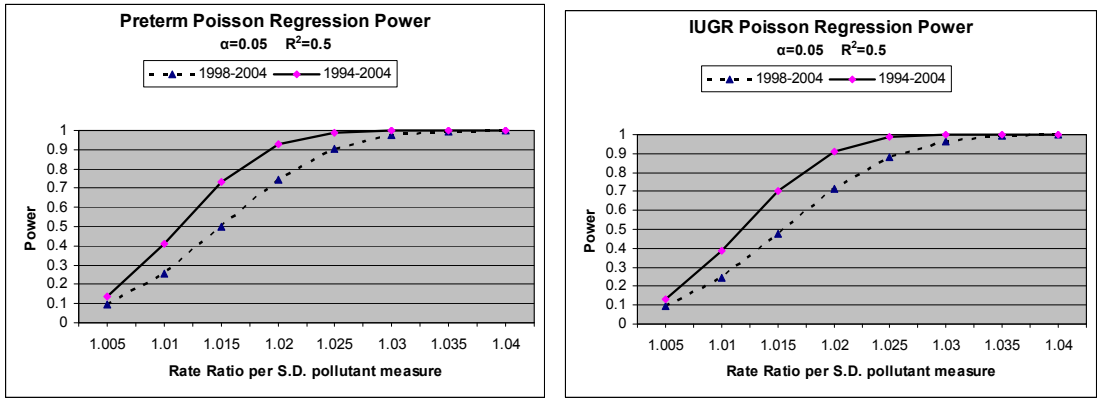
approximating personal exposure with ambient levels of air pollution by incorporating published estimates of the relationship of personal to ambient levels for various pollutants from the literature (Ebelt et al., 2000; Janssen et al., 1998).

Power Calculations

Statistical power is a major strength of this project. With a study size of approximately 550,000 births, this project has three times the number of births relative to the largest previous investigation of preterm birth and air pollution (Sagiv et al., 2005). In analyses limiting the study period to years for which $PM_{2.5}$ and detailed particle speciation is available (August 1998-2004) the 320,000 births available is still twice that of the next largest study population. Of studies examining measures of fetal growth (including crude birth weight), this study has 160,000 more births than the largest sample size of 388,000 births (Lee et al., 2003).

Power was calculated for our primary analytic strategies for each outcome using PASS software (NCSS Statistical Software, 2005), with the probability of a type 1 error fixed at $\alpha=0.05$ (two-sided hypothesis) and the coefficient of multiple determination for the covariates regressed on the air pollution measurement fixed at $R^2=0.50$. The rate ratios presented correspond to a 1-standard deviation increase in the value of the pollution measurement so that pollutant effects can be compared on a similar scale. Sample sizes are based on an average rate of 50,000 births per year in the five-county Atlanta area. Data limitations such as availability of LMP may slightly decrease these power estimates. However, to be conservative we have calculated power based on two-sided hypotheses despite the fact that we do not expect to find a protective effect of air pollution on these birth outcomes.

Figure 3.8. Power curves for preterm birth and IUGR



Preterm delivery. Of the 50,000 births per year in the five-county Atlanta approximately 11% are premature (Georgia Division of Public Health). On average this leads to 137 births per day, 15 of which are born premature. Assuming a study size of 4018 days over the period 1994-2004 and 2312 days over the period from August 1998-2004, power graphs are presented above. Over the study period 1994-2004 we have 80% power to observe a rate ratio of 1.016, power is 95% to detect a rate ratio of 1.021. For the sub-period 1998-2004 during which we have more detailed PM measurements, we have 80% power to observe a rate ratio of 1.022 and 95% power to observe a rate ratio of 1.028. Using the standard deviations of PM_{10} levels reported in the two previous US studies, rate ratio estimates for preterm delivery ranged from 1.01 to 1.06 for a one standard deviation increase in PM exposure (Ritz et al., 2000; Sagiv et al., 2005).

IUGR. In the small for gestational age analysis our primary analysis also employs a temporal Poisson model. Using the national reference, approximately 10% will be considered small for gestational age. This leads to approximately 14 out of 137 births per day designated as SGA. Over the study period 1994-2004 we have 80% power to observe a rate ratio of 1.017; power is 95% to detect a rate ratio of 1.022. For the sub-period 1998-2004, we have 80% power to observe a rate ratio of 1.022 and 95% power to observe a rate ratio of 1.029. A recent NCHS/USEPA collaboration was the first US study to examine $PM_{2.5}$ levels in relation to IUGR;

the odds ratio for an approximate 1 standard deviation increase in third trimester exposure was 1.12. (Parker et al., 2005)

Low birth weight. With approximately 9% of births in five-county Atlanta born weighing less than 2500 grams (Georgia Division of Public Health), power graphs for crude low birth weight are very similar to those for the two primary birth outcomes presented above. We expect approximately 12 of 137 births per day to be low birth weight. For the period 1994-2004, we have 80% power to observe a rate ratio of 1.018, power is 95% to detect an odds ratio of 1.024. For the sub-period 1998-2004, we have 80% power to observe an odds ratio of 1.024 and 95% power to observe a rate ratio of 1.031.

For all three birth outcomes, we have sufficient power to observe the range of effects reported in previous US studies. Even small effects would have significant public health implications due to the large number of individuals exposed to air pollution and the high prevalence of these birth outcomes in the US population. Furthermore, the point estimates reported in these power calculations are based on a one standard deviation increase in pollutant measure; the range of exposure experienced extends well beyond one standard deviation.

Manuscripts to be developed

As part of this dissertation, three manuscripts will be prepared for publication in the epidemiologic literature. The first manuscript will describe seasonal patterns of birth in the study population and the methodological implications for temporal investigations of adverse pregnancy outcomes. The issues described in this first manuscript set the stage for the investigation of seasonally varying air pollution exposures presented in the following two manuscripts. In the second manuscript, results from the temporal analyses of air pollution and preterm birth will be presented. This study will address the primary and secondary hypotheses for preterm birth, investigating levels of gaseous and particulate air pollutants during the six weeks before birth, the one week before birth and the first month of gestation in relation to rates of preterm birth. In the third manuscript, primary and secondary hypotheses for SGA will be investigated; temporal associations between SGA and gaseous and particulate air pollutants during the third trimester as well as the first month of gestation will be presented.

CHAPTER 4

Seasonality of birth in Atlanta and implications for temporal studies of preterm birth

[Formatted for *Epidemiology*]

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ABSTRACT

Background: It is well known that birth rates exhibit seasonal variation, and there is some evidence to suggest that such seasonal variation in birth rates can differ among socio-demographic subgroups. We examine these seasonal birth patterns and whether they could confound temporal investigations of seasonally varying exposures and preterm birth. **Methods:** The study cohort consisted of all births in 20-county metropolitan Atlanta delivered during 1994-2004 (n=715,875). We identified months with higher and lower than expected number of births for the overall birth cohort and in subgroups stratified by socio-demographic factors. We then explored whether the seasonal patterns of birth could lead to artifactual seasonal differences in observed rates of preterm birth. **Results:** The overall seasonality of birth reached a peak in births in August-September and a trough in April-May. The most meaningful differences in seasonality were observed across levels of maternal education, race/ethnicity and marital status. Maternal age groups and primiparity status showed less divergent patterns of birth seasonality. These seasonal patterns of birth led to small differences in the expected rate of preterm birth across calendar months. **Conclusions:** In metropolitan Atlanta between 1994 and 2004, we observed seasonal patterns of birth which differed among socio-demographic subgroups. These patterns lead to seasonal heterogeneity in the pregnancies at risk for preterm birth and thus warrant consideration in temporal studies of seasonally varying exposures and preterm birth.

INTRODUCTION

Seasonal patterns of birth have been observed in human populations for almost two centuries.[1,2] Many cultural, biological and environmental factors are hypothesized to contribute to these seasonal patterns which differ by geographical location and time. Over the past 50 years, the annual pattern of births in the US has been characterized by a peak in August-September and a trough in April-May, with southern latitudes tending to show a deeper spring trough.[3-5] Temperature is thought to be partially responsible for this pattern, with high summer temperatures reducing conceptions either through reduced coital frequency or decreased fecundability (e.g., decreased sperm quality).[4-6] Other factors which may contribute to the annual pattern of birth include photoperiod (day length), increases in coital frequency during holidays, seasonal wedding preferences, seasonal patterns in fetal loss, and seasonal preferences in pregnancy planning.[7-10]

The factors thought to drive seasonality may differ among socio-demographic groups, leading to different seasonal patterns of birth among population subgroups. For example, less affluent groups may have less access to air conditioning, work in occupations with more exposure to outdoor light and temperature, and have different patterns of contraceptive use. The literature, although more sparse on this topic, suggests that the seasonality of birth in the US is more pronounced in low socioeconomic groups, with higher peaks in the summer and lower troughs in the spring.[11-13] Data from Europe also suggests that lower social class may be associated with fewer spring births.[14]

These seasonal patterns of birth may have implications for the study of preterm birth (birth before 37 completed weeks of gestation). Several studies have used a time-series approach to examine seasonality in the rate of preterm birth or to examine the relationship between a specific seasonally-varying exposure and preterm birth.[15-19] Many hypothesized mechanisms of preterm birth lend themselves well to a time-series design; temporal spikes in various types of infection, air pollution, allergen levels, pesticide application, water quality and meteorological factors can be examined in relation to short-term changes in the rate of preterm birth. In the

typical time-series analysis, daily counts of the outcome are compared across time, under the assumption that underlying risk in the population is constant through time. In contrast, the risk set in a time-series analysis of birth outcomes is constantly changing throughout the study period according to who is at risk (i.e., pregnant) at a given time. Thus time-series analyses in pregnancy cohorts require additional considerations not necessary in many time-series applications.

Because the risk set of pregnancies in a time-series analysis is constantly changing, seasonal patterns of birth may drive seasonal differences in underlying risk of preterm birth. When examining rates of preterm birth across time, one approach has been to identify daily (or monthly, etc.) counts of preterm birth (numerator) and the number of ongoing gestations at risk of preterm birth (denominator).[16,17,19] If we consider the risk set to be comprised of ongoing gestations between 20 and 36 weeks of gestation, seasonality of birth would lead to different distributions of gestational age in the risk set at different times of year. For example, as the peak birth season approaches, the gestational age distribution in the risk set of ongoing gestations would be more heavily weighted toward later gestational ages, when the risk of preterm birth is greater. Likewise, differences in seasonality of birth between high and low risk socio-demographic groups would lead to seasonal differences in the distribution of high and low risk pregnancies in the risk set at different times of the year.

As a result of these seasonal patterns of birth, observed differences in the rate of preterm birth across seasons may indicate seasonal etiologic influences on the counts of preterm birth (the numerator), or they may reflect uncontrolled differences in underlying risk in the pregnancy risk set (the denominator) across seasons. In this paper we first describe the seasonal patterns of birth in metropolitan Atlanta over the period 1994-2004. We examine the seasonal pattern of birth in the full cohort and for several socio-demographic subgroups. We then explore the potential for confounding by the observed seasonal patterns of birth in a time-series investigation of seasonally varying exposures and preterm birth.

METHODS

We obtained vital records for births to residents of the 20-county Atlanta metropolitan area over the years 1994-2004 from the Georgia Division of Public Health, Office of Health Information and Policy. Using this cohort, we considered three separate issues. First we assessed the overall seasonality of birth in the full cohort. Second, we investigated possible differences in seasonal patterns of birth among socio-demographic subgroups. Third we investigated whether the seasonal trends observed in the first two analyses could induce apparent seasonality in the rate of preterm birth, even in the absence of seasonal etiologic influences.

Overall seasonality of birth

We began by plotting the average number of births per day in each study month to visually assess seasonal (i.e., calendar month) and long term birth trends through the study period. To quantify the magnitude of seasonal fluctuation in birth rates, we created a ratio of observed to expected number of births for each month of the study.[4,5] The observed number of births per day was the average number of births per day in each study month. The expected number of births per day was calculated using a centered 12-month moving average comprised of the 5.5 months before, the month of interest, and the 5.5 months after. Thus, the expected count contained no seasonality. The observed/expected ratio filtered out the variation in birth rates due to long term trends and allowed us to examine the seasonal variation in birth rates without forcing a specific shape to the seasonal pattern across calendar months.[4,5] There were 120 study months included in the analyses, July 1994 through June 2004; expected numbers of births could not be calculated for the first 6 months and final 6 months of the study period because a 12-month moving average could not be calculated. Observed/expected ratios were plotted by year and summarized by averaging across years by calendar month.

Seasonality of birth by socio-demographic subgroup

Only births with complete data on the socio-demographic factors of interest were included in the population subgroup analyses. We examined available socio-demographic factors known to be associated with preterm birth: maternal race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, Asian), maternal age (<20, 20-34, 35+), marital status (married, unmarried), maternal education (less than 12 years, 12-15 years, 16+ years), and parity (first birth vs. second or greater birth). To compare the seasonality of birth across levels of socio-demographic characteristics, the birth cohort was stratified by the characteristic of interest, and a ratio of observed to expected births per day was calculated for each study month (July 1994-June 2004) within each stratum. To assess whether seasonality of birth differed by maternal race, for example, we regressed the observed/expected births on calendar-month indicator variables, maternal race indicator variables, and interaction terms between race and calendar month. The significance of interaction terms was assessed using an F-test after verifying the independence of the residuals with the Durbin-Watson test. The model took the form:

$$\ln(Y_{ij}) = \alpha + \beta_1(Jan_i) + \beta_2(Feb_i) + \beta_3(Mar_i) + \beta_4(Apr_i) + \beta_5(May_i) + \beta_6(Jun_i) + \beta_7(Jul_i) + \beta_8(Aug_i) + \beta_9(Sep_i) + \beta_{10}(Oct_i) + \beta_{11}(Nov_i) + \sum_{n=1-3}(\chi_n)(race_j) + \sum_{m=1-33}(\pi_m)(month_i * race_j) + \varepsilon_{ij}$$

Y_{ij} represents the observed/expected births per day in study month i within race/ethnicity stratum j. The product terms allow for possible interaction between maternal race and birth seasonality (i.e., calendar month). We constructed analogous models for maternal age, marital status, educational status, and parity, and we plotted the regression estimates of observed vs. expected births for each calendar month within each socio-demographic group. Calendar month dummy variables were coded such that estimated effects for each month were expressed relative to the average of all months.

Seasonal birth patterns and preterm birth

Next, we investigated if the seasonal patterns observed in the previous analyses could act as confounders in time-series analyses of a seasonally varying exposure and preterm birth. To calculate rates of preterm birth over time, the preterm birth counts must be related to an appropriate denominator.

One possible approach is to divide the count of preterm births in one calendar month by the number of live births in that month. Previous authors have noted that this approach can be misleading; using live births as the denominator may generate apparent seasonality in the rate of preterm birth due to the seasonality of conceptions.[15-18] A preferred approach is to relate counts of preterm birth to ongoing pregnancies at risk of preterm birth, so that the denominator is comprised of *in utero* fetuses within a range of gestational ages (e.g., between 20 and 36 weeks gestation).[16,17,19] Although this approach is an improvement over using live births as a denominator, seasonality of birth remains an issue, because some months will be more heavily weighted toward 36 week old fetuses, whereas other months will be more heavily weighted toward 20 week old fetuses. More preterm births would be expected to occur in the months when the risk set is more heavily weighted toward the 36 week olds. Likewise, if high and low risk population subgroups have different seasonal patterns of birth, this could also lead to apparent seasonal differences in the rate of preterm birth, even in the absence of any seasonal etiology.

We used the Atlanta 1994-2004 birth cohort data to quantify the potential for confounding if these seasonal differences in composition of the risk set are ignored. For each study day we identified the risk set of all ongoing gestations between 20 and 36 weeks using the birth date and gestational age of each newborn. For 98.2% of birth records, the reported last menstrual period (LMP) date yielded a plausible gestational age at birth between 20 and 44 weeks; for these records we used the LMP date to calculate gestational age. For 1.7% of births, the clinician's estimate of gestational age was substituted for a missing or implausible LMP date, and for the 0.1% of observations missing both LMP date and clinical estimate, we used a

gestational age imputed by the Georgia Division of Public Health based on the birth weight of the infant.

To quantify the influence of the seasonally changing gestational age distribution of the risk set on the expected rates of preterm birth, our approach was as follows:

1) We calculated conditional probabilities of birth at every gestational week between 20 and 36 weeks using the gestational age of each infant in the birth cohort (i.e., probability of birth at 21 weeks=

p [21 weeks ≤ birth < 22 weeks | birth ≥ 21 weeks]). The conditional probabilities are shown in Table 4.2. We assumed that the risk of birth was constant across the seven days of each gestational week.

2) For each study day, we calculated the *expected* count of preterm births by multiplying the probability of birth at each gestational week by the number of fetuses at the corresponding gestational week on that day (we divided the conditional probability of birth for each gestational week by seven to get daily probabilities).

3) For each study day, we identified the number of fetuses at risk of preterm birth, i.e., the aggregate number of fetuses *in utero* between 20 and 36 gestational weeks.

4) Expected counts of preterm birth were summed by calendar months (i.e., across all Januaries), as were the total number of fetus-days at risk for each of the calendar months. Using this information we calculated an average expected risk per fetus per day for each calendar month.

5) Risk ratios comparing average expected risk of preterm birth between calendar months were calculated to quantify the seasonal variation in expected risk of preterm birth when the changing gestational age distribution of the risk set is ignored.

We conducted a similar analysis to investigate whether seasonal changes in the socio-demographic composition of the risk set could drive seasonality in preterm birth rates. For this analysis, we stratified the dataset according to race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Asian) and aggregated births according to conception date (assumed to be 14

days after LMP). Thus, each stratum-specific risk set included all conceptions on a given date who eventually reached at least 20 weeks gestation (intrauterine fetal deaths before week 20 are not recorded in our dataset). Although similar analyses could be conducted for other socio-demographic variables, we focused on race/ethnicity, a strong risk factor for preterm birth. For each conception date during the study period we calculated an expected count of preterm births based on the racial distribution of fetuses in the risk set and the race-specific risks of preterm birth. Because black infants have an overall greater risk of preterm birth than other race groups (15.4% vs. 10.3% for white infants in our study population), a conception day with a higher percentage of black fetuses in the risk set would lead to a higher proportion of preterm births. Total conceptions and expected counts of preterm birth were summed by calendar month (all Januaries, Februaries, etc.), and an average expected preterm risk was calculated for each calendar month. Risk ratios comparing average preterm birth risk between calendar months were calculated to quantify the difference in risk attributable solely to seasonal changes in the racial composition of the risk set.

RESULTS

The metropolitan Atlanta 1994-2004 pregnancy cohort consisted of 715,875 births; characteristics of the population are presented in Table 4.1. Due to missing data, 2.24% of births were excluded from the maternal education analysis, 0.02% were excluded from the marital status analysis, and 1.61% were excluded from the parity analysis. The 0.35% of births categorized as "American Indian," "Hawaiian/Other" or "Multiracial" were also excluded due to insufficient numbers.

Overall seasonality of birth

Average numbers of births per day for each study month are shown in Figure 4.1; seasonal as well as long term trends are evident. The average ratios of observed to expected

number of births by calendar month are presented in Figure 4.2. Monthly observed vs. expected births for individual study years are also included in the plot and demonstrate the strong consistency of the seasonal pattern. Births in July, August and September were 2-5% higher than expected; births in April, May, June, November, and January were 2-3% lower than expected.

Seasonality of birth by socio-demographic subgroup

Model-based monthly ratios of observed to expected births by socio-demographic group are presented in Figures 4.3-4.7. The largest differences in seasonality of birth were observed across levels of maternal education, maternal race/ethnicity and maternal marital status. Notably, the college-educated group showed a peak in spring births as opposed to the trough seen in the two less-educated groups. The largest April-May troughs observed were in the unmarried, less than high school, black and Hispanic groups. The college-educated, married, and white groups showed a large trough in births in November, December and January. Of all the socio-demographic strata examined, the Hispanic group showed the largest seasonal amplitude in births, with 7% fewer births than expected in May and 7% more births than expected in September. All socio-demographic strata examined showed higher than expected numbers of births in August and September. Differences in seasonality of birth between maternal age groups and between parity groups were less pronounced; however, F-tests for the interaction terms between all socio-demographic factors and calendar months were significant ($p<0.0001$). All plots showed consistent seasonal patterns across study years (Appendix A).

Seasonal birth patterns and preterm birth

Gestational week-specific conditional probabilities of birth are displayed in Table 2. Risk of (preterm) birth increases dramatically with gestational age, particularly between week 33 and week 36. Shown in Figure 4.8 are the risk ratios comparing average fetal risk in each month versus the risk in May, the month of lowest fetal risk. The seasonal pattern of risk mirrored that of

the overall seasonality of birth; the pattern was consistent across years (Appendix A). Based entirely on the gestational age distribution of the risk set, average risk of preterm birth per fetus was highest in late summer, just before the August-September peak in births, when the risk set was more heavily weighted toward later gestational ages. Likewise, there was a trough in risk in May, when fewer fetuses were in late gestation. The risk ratio comparing August to May was 1.077, suggesting an expected 7.7% increase in preterm birth in August compared to May attributable solely to seasonal changes in the gestational age distribution of the risk set. In other words, in the absence of any true seasonal etiology, if the gestational age distribution of the risk set is ignored, risk of preterm birth would appear 7.7% higher in August compared to May.

The risk of preterm birth varied by race/ethnicity: 15.4% for black infants, 10.3% for white infants, 9.2% for Hispanic infants, and 9.6% for Asian infants. As our previous analyses demonstrate, different races/ethnicities show different patterns of birth seasonality. Of the conceptions who reach 20 weeks of gestation in Atlanta, the proportion who are black is 2.7% higher in March than in July. Because African Americans have an elevated risk of preterm birth, this translates into an average 1% increase in the risk of preterm birth (RR=1.01) for fetuses conceived in March compared to July when race/ethnicity is ignored. Shown in Figure 4.9 are the risk ratios comparing the expected risk of preterm birth for fetuses conceived in each month relative to July, the month of lowest risk; these risk ratios reflect seasonal differences in underlying risk of preterm birth based solely on the racial composition of the risk set. Composition of the risk set with regard to other socio-demographic characteristics such as maternal education and marital status may enhance or dampen these seasonal differences in underlying risk of preterm birth.

DISCUSSION

In the 20-county Atlanta 1994-2004 cohort, we found the expected risk of preterm birth to vary as much as 7.7% based on the gestational age distribution of the risk set and 1% based on

the racial composition of the risk set. Although these effects are small, they are important to consider in large registry-based studies which are statistically powered to detect small effects. Furthermore, small effects can have large public health impacts, particularly when the exposure and outcome are both common (e.g., an investigation of the relationship between ambient air pollution levels and risk of preterm delivery). In this analysis we only examined the racial composition of the risk set; the joint effects of other seasonal socio-demographic patterns may be larger. Alternatively, competing seasonal trends may negate each other. The magnitude of variation will be population dependent and may be more or less extreme in populations with different socio-demographic compositions and different seasonal patterns of birth.

Ignoring the gestational age distribution or socio-demographic composition of the risk set may induce or obscure an association between preterm birth and a seasonally varying exposure, or season itself. For example, if ambient levels of air pollution are highest in August (e.g., ambient fine particulate matter in Atlanta is generally highest in late summer, data not shown), air pollution may look predictive of preterm birth only because the risk set in August is most heavily weighted toward later gestations. This bias is attributable to grouping a wide range of gestational ages in the risk set despite later gestational ages have dramatically higher risk of birth. One way to avoid this issue is to investigate exposures at specific gestational windows of susceptibility, when fetuses are aggregated at a specific gestational age (e.g., at conception). However, investigations of acute exposures thought to trigger preterm labor likely require evaluating exposure windows defined relative to the birth date as opposed to a specific gestational age; these time-series investigations will require proper accounting for the gestational age distribution of the risk set to avoid the potential for confounding by birth seasonality. Contrasting rates of preterm birth across time within gestational week strata is recommended given that risk of birth increases dramatically with each gestational week. We provide an example of this method in our study of ambient air pollution and preterm birth in the Atlanta 1994-2004 cohort (see Chapter 5).

In contrast to the gestational age distribution, seasonal differences in the socio-demographic composition of the risk set is an issue regardless of whether the risk set is limited to fetuses at a specific gestational age or contains a range of gestational ages. If high and low risk population subgroups for preterm birth exhibit different seasonal patterns of conception and birth, temporally modeling counts of preterm birth within the high and low risk strata may be necessary. A limitation of this approach is that data on some seasonally varying risk factors for preterm birth may not be available. If season itself is not the exposure of interest, controlling for season as a proxy of unavailable seasonally varying factors is an option, although the appropriate form of seasonal control is not always apparent. In our analyses the annual trends did not fit neatly into fall, winter, spring and summer categories and would require more stringent seasonal control. Ultimately season is only a proxy for a number of factors that, if available, can be handled directly in the analysis.

This study also contributes to the descriptive literature on seasonal birth patterns using a contemporary cohort. In the full cohort of births in 20-countyAtlanta between 1994 and 2004, we observed a seasonal pattern of birth characterized by a peak in late summer/early fall and trough in spring. We observed the largest spring troughs in births in groups associated with lower socioeconomic status: the less than high school education, unmarried, black and Hispanic groups. Women with at least 16 years of education also exhibited strong seasonality of birth, but with a markedly different pattern from lower educational strata. Births in this group showed a peak in March-May, a second peak in September, and a large trough in November-January. Of the socio-demographic subgroups examined, the Hispanic group showed the greatest amplitude of birth seasonality.

Lam and Miron (1996) previously reported a similar overall pattern of birth rates for Georgia during 1942-1988 but with a greater seasonal amplitude, 7-10% more births than expected in August-September and 7-10% fewer births in April-May.[4] In general, the seasonal amplitude in birth rates in the US appears to be greater for southern states compared with

northern states, and this is thought to be partially due to higher summer temperatures in the south.[1,3,4,9] Animal and human studies suggest that high temperatures interfere with spermatogenesis and subsequent fertility; lower sperm quality in the summer could explain reduced birth rates in the spring.[6,20] The observed peak in births in late summer/early fall is more difficult to explain than the observed spring trough. Some speculate that the holiday season, and its associated increase in family and leisure time, may lead to an increase in coital frequency. However, the August-September peak in births has also been observed in populations not subject to the holiday effect.[7] In contrast to the US, the pattern of birth in Europe peaks in the spring and declines in the fall. It is possible that increased coital frequency during summer holidays in Europe counteract any decrease in fertility due to high temperatures.[1,4] Photoperiodicity, supported by both human and animal data, also likely plays a role in seasonal birth patterns particularly in places with large seasonal variations in day length. [4,6,9,21] A myriad of other cultural and biological factors could also influence the timing of conception and subsequent birth. Furthermore, the seasonality of birth may be partially influenced by seasonal patterns in fetal loss, not just seasonal patterns of conception.[10]

Differences in exposure to the factors thought to drive overall seasonal patterns of birth could explain differences in seasonality between socio-demographic groups. For example, we observed the strongest seasonal pattern of birth in Hispanics. In Atlanta, approximately 50% of Hispanic males work in the construction industry, an occupation involving constant exposure to outdoor temperature and light.[22] A previous study from 1979 in Fulton County, Georgia, one of the 20 counties included in this analysis, which found that women living in low income census tracts showed a greater degree of birth seasonality.[12] More recently in Texas, Chandwani and colleagues reported that the amplitude of the seasonal pattern varied inversely with years of maternal education, a proxy measure of socioeconomic status.[13] The spring trough of births observed in this study in the lowest educational stratum is consistent with these previous findings. However, we also observed strong seasonality in the highest educational stratum, but with a

spring peak instead of trough. Because a greater percentage of births in this group are planned, this pattern may more closely reflect the preferred timing of birth.[23] There is evidence that summer is the preferred time to start pregnancy, and February-March is the least preferred time.[8,24] Data from the Czech Republic also suggests that the typical peak in spring births is more enhanced in women who are married and have a university education.[14] If indeed the preferred season of birth for pregnancy planners is spring, a greater proportion of planned pregnancies in European populations could explain some of the difference in overall birth pattern between the Europe and the US.

The seasonal patterns of birth described offer clues to seasonal influences on human fertility, but they also have important implications for time-series analyses of adverse pregnancy outcomes. The observed seasonal patterns of birth, and consequent seasonal patterns in the gestational age and socio-demographic composition of the pregnancy risk set, led to seasonal differences in the risk of preterm birth. Future temporal studies of preterm birth in relation to seasonally varying exposures should consider the potential confounding introduced by seasonal patterns of conception and birth.

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Table 4.1: Maternal and infant characteristics the 20-county Atlanta metropolitan area 1994-2004 birth cohort

	Births (%) N= 715,875
Preterm (<37 weeks gestation)	84,559 (11.8%)
Maternal Age	
<20 years	75,377 (10.5%)
20-34 years	539,112 (75.3%)
35+	101,386 (14.2%)
Years of Maternal Education	
Under 12	134,920 (19.3%)
12	195,583 (28.0%)
13-15	149,142 (21.3%)
16 or more	220,220 (31.5%)
Singleton	693,159 (96.8%)
Female	350,656 (49.0%)
Married	484,952 (67.8%)
Parity	
1	304,697 (43.3%)
2	229,888 (32.6%)
3+	169,734 (24.1%)
Race/Ethnicity	
White	374,818 (52.4%)
Black	230,985 (32.3%)
Hispanic	80,644 (11.3%)
Asian	26,876 (3.8%)
American Indian	156 (0.02%)
Hawaiian/other	1,217 (0.17%)
Multiracial	1,179 (0.16%)

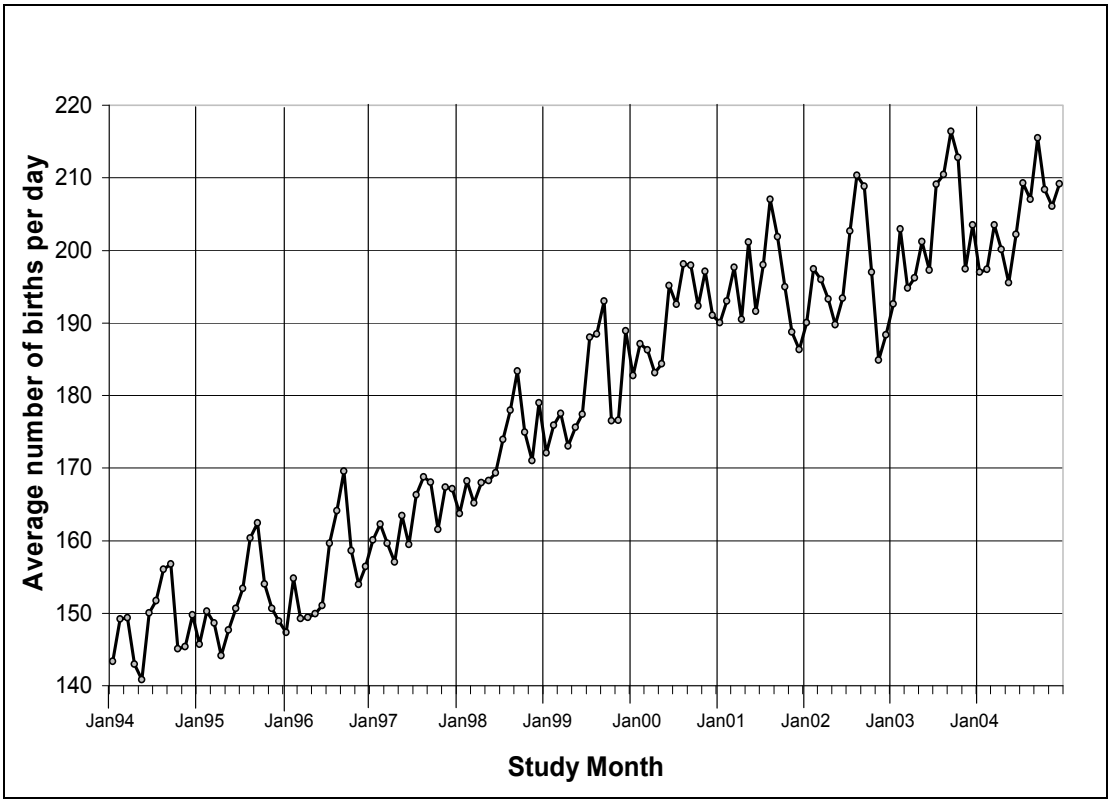

Figure 4.1. Average number of births per day by study month, January 1994-December 2004

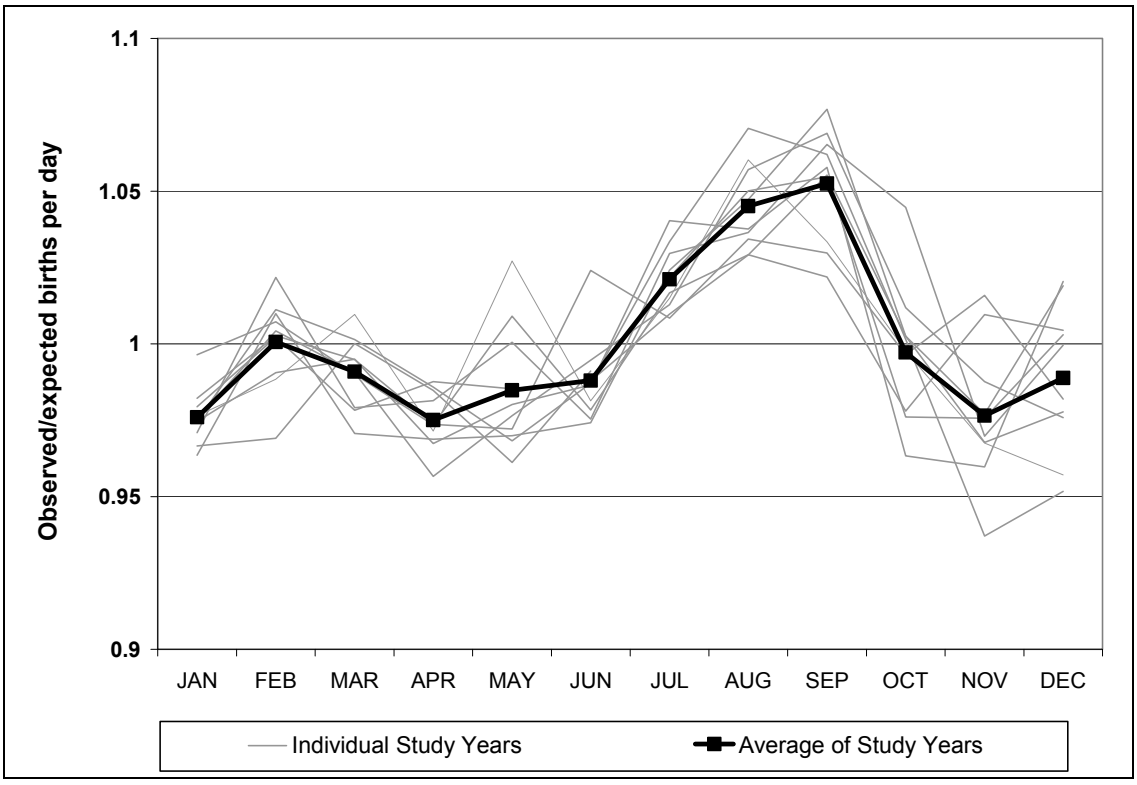

Figure 4.2. Seasonality of birth in the 20-county Atlanta metropolitan area 1994-2004: average observed/expected births per day by calendar month and monthly observed/expected births per day for individual study years. Expected births per day are based on a 12 month moving average of current month, previous 5.5 months and following 5.5 months.

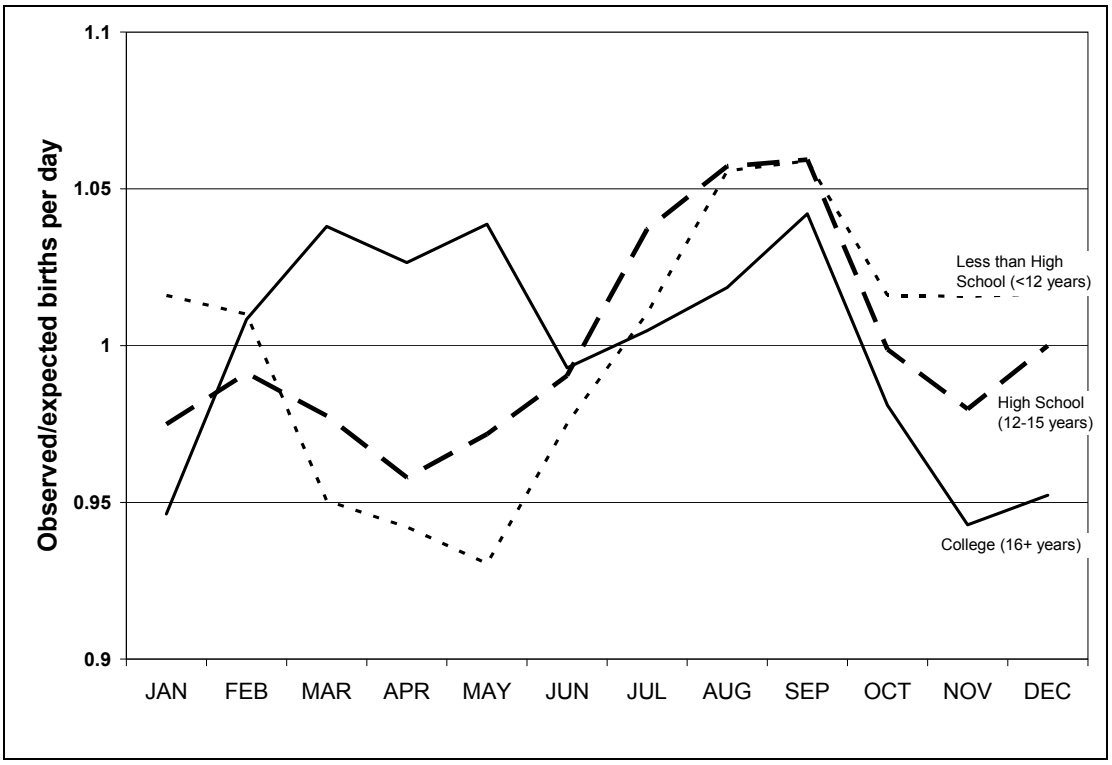

Figure 4.3. Model based estimates of observed/expected births per day by calendar month, stratified by maternal education level.

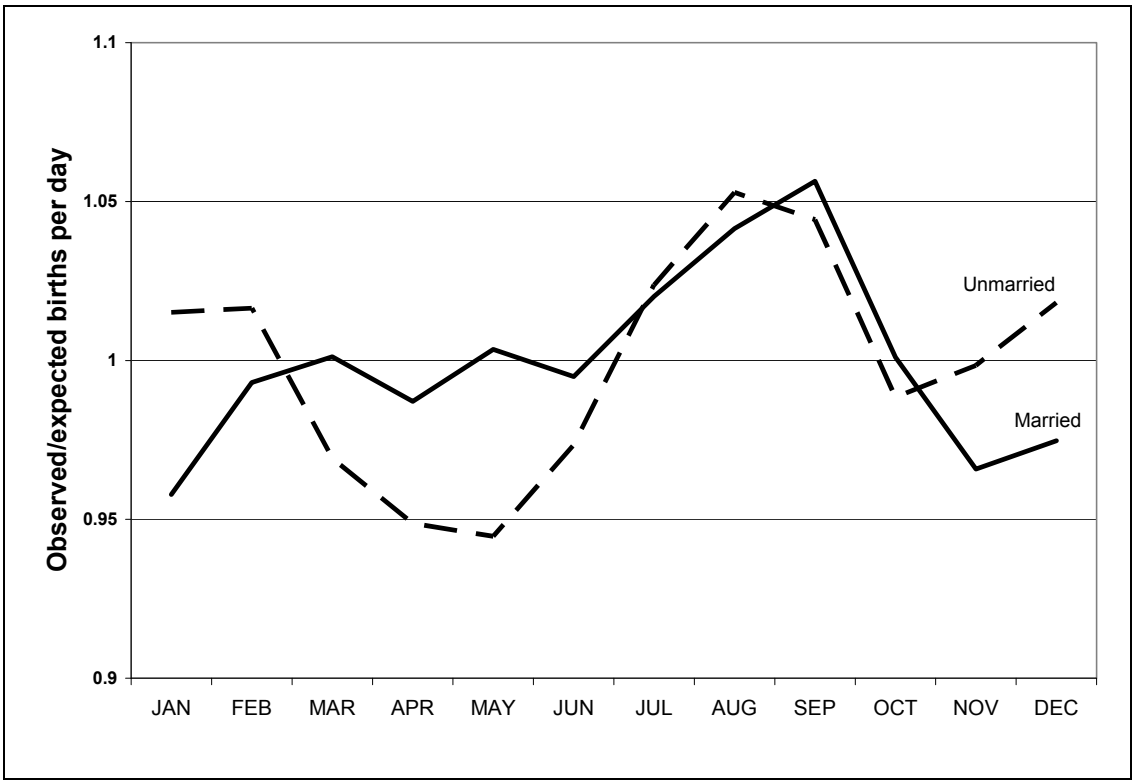

Figure 4.4. Model based estimates of observed/expected births per day by calendar month, stratified by maternal marital status.

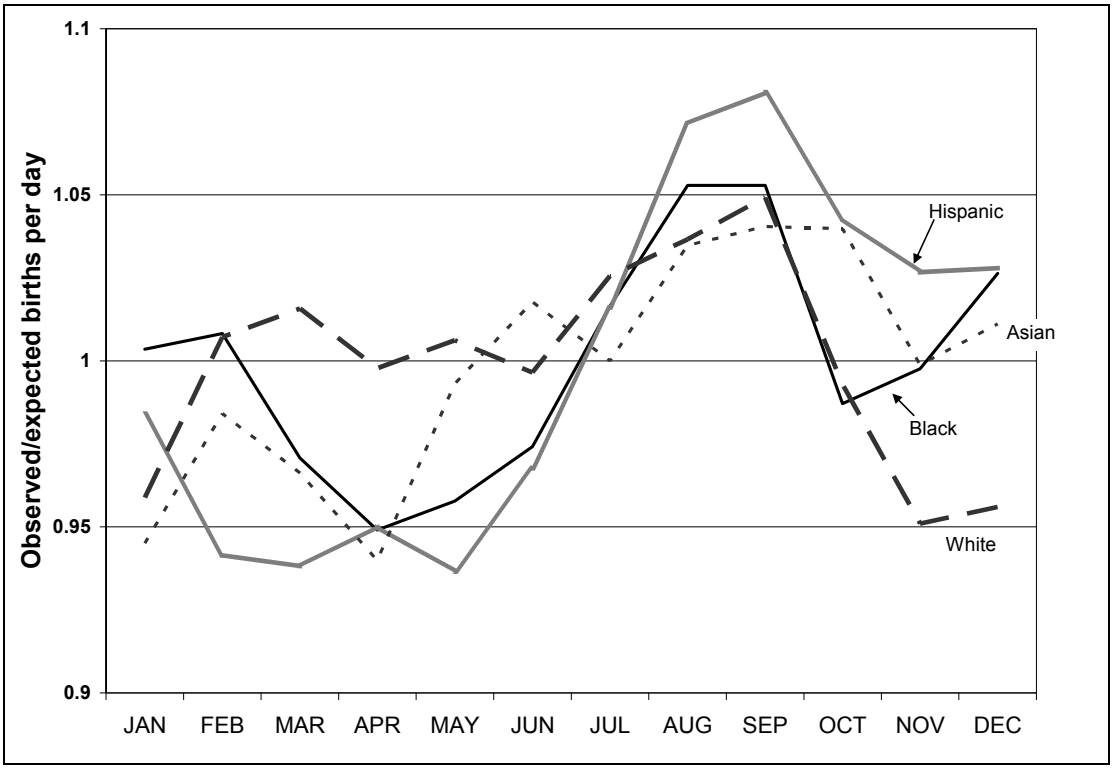

Figure 4.5. Model based estimates of observed/expected births per day by calendar month, stratified by maternal race/ethnicity.

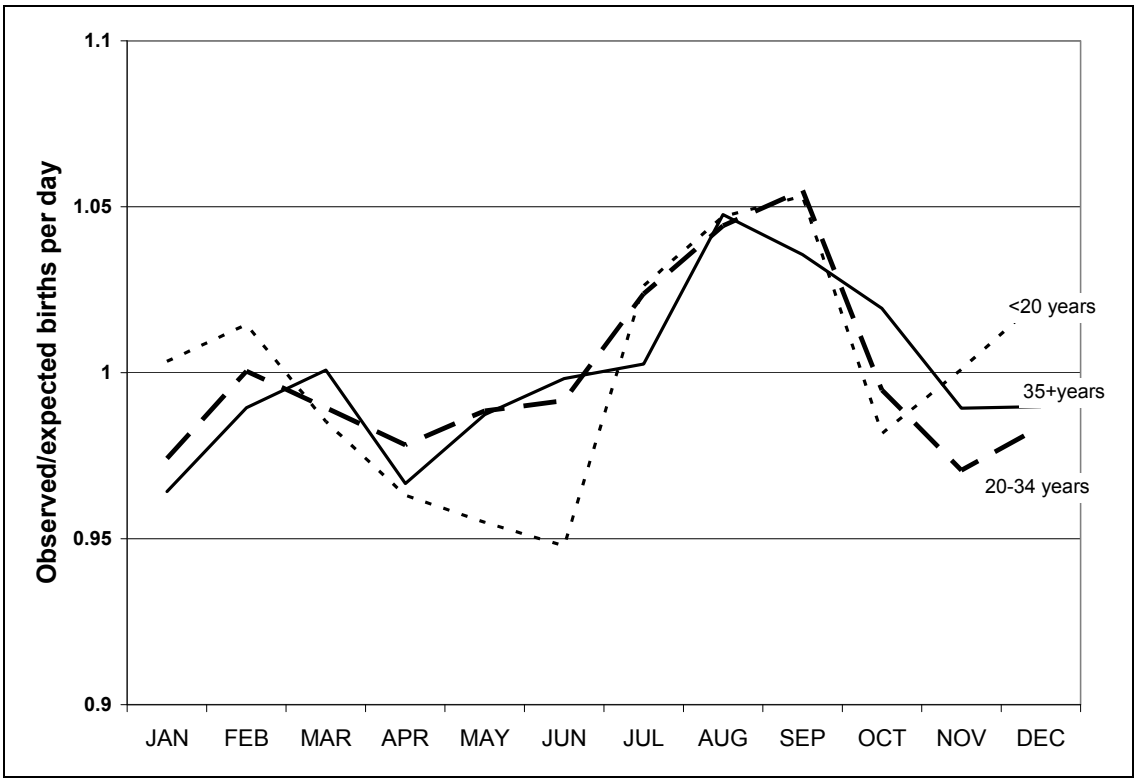

Figure 4.6. Model based estimates of observed/expected births per day by calendar month, stratified by maternal age group.

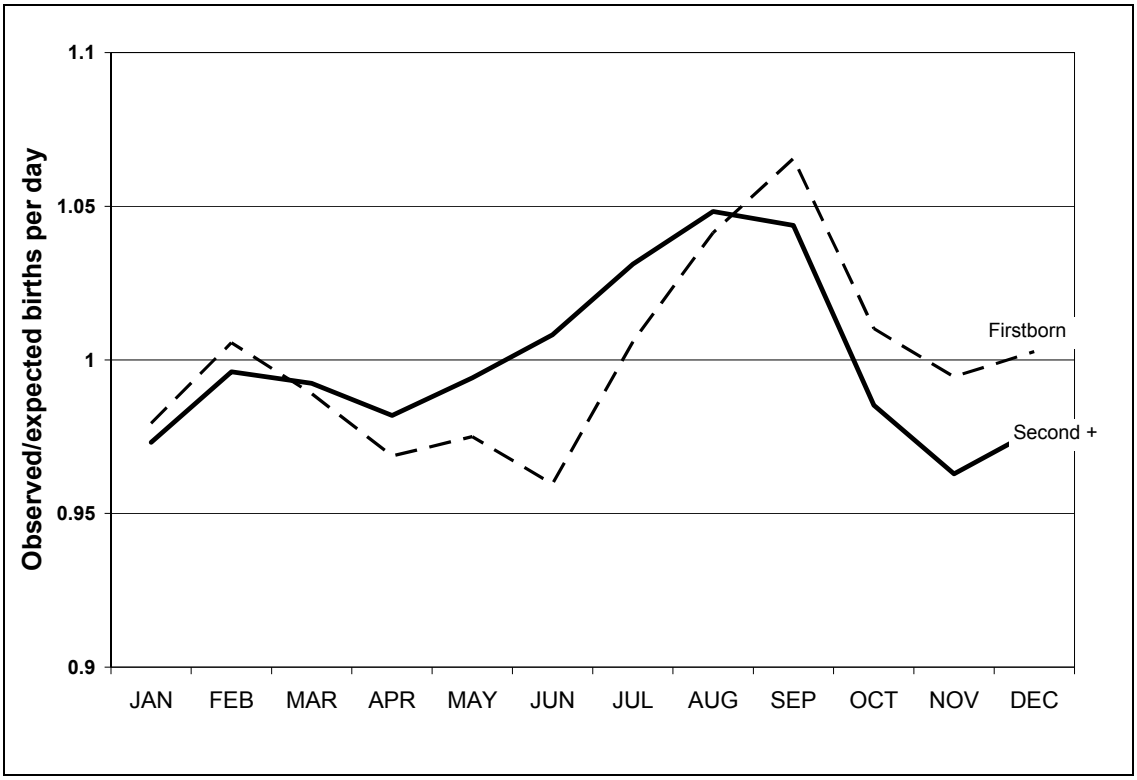

Figure 4.7. Model based estimates of observed/expected births per day by calendar month, stratified by primiparity status.

Table 4.2. Probability of preterm birth at each gestational week before 37 weeks (i.e., full term). Probabilities are calculated conditional on reaching the gestational week of interest.

Gestational Week	Probability
20	0.00038
21	0.00045
22	0.00087
23	0.00095
24	0.00121
25	0.00147
26	0.00165
27	0.00169
28	0.00205
29	0.00236
30	0.00320
31	0.00396
32	0.00584
33	0.00861
34	0.01496
35	0.02632
36	0.04801

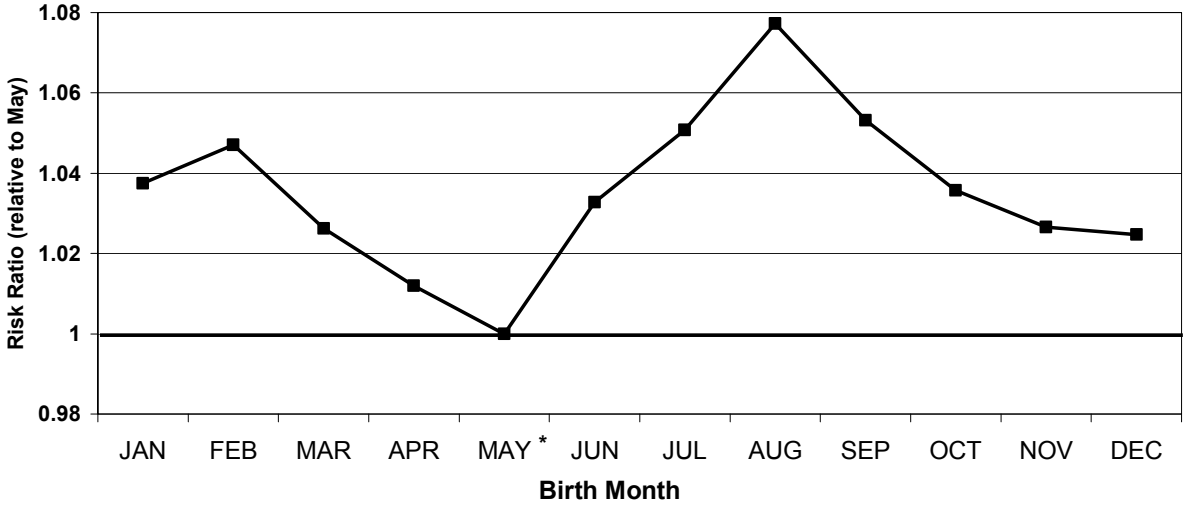

Figure 4.8. Risk ratios comparing expected daily risk of preterm birth per fetus in each calendar month relative to May*, the month of smallest risk, based solely on the gestational age distribution of the risk set.

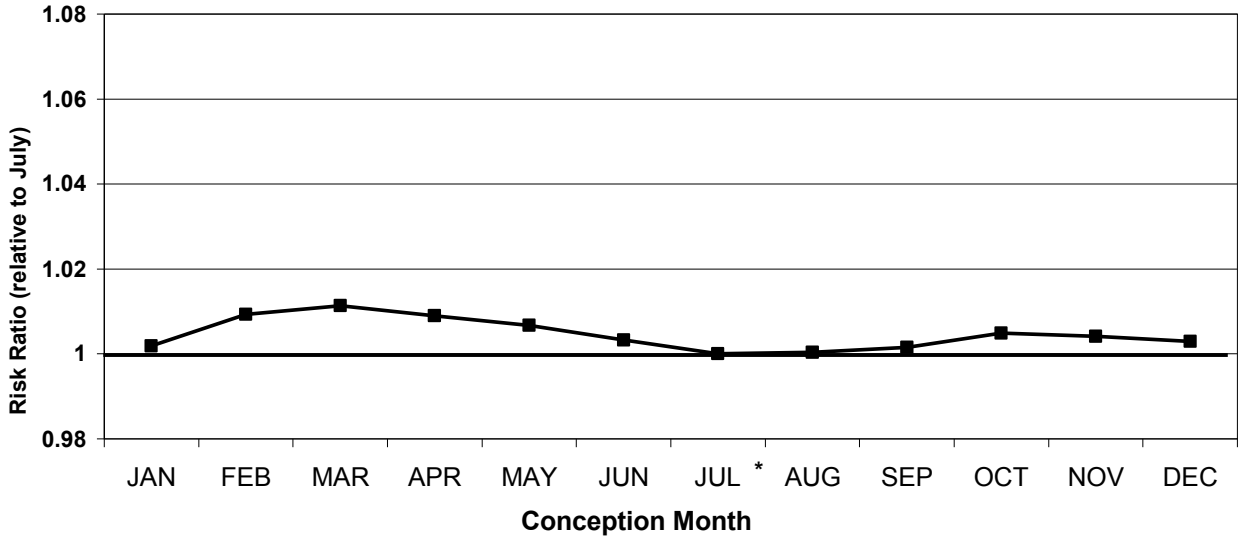

Figure 4.9. Risk ratios comparing expected risk of preterm birth for fetuses conceived in each month relative to July*, the month of smallest risk, based solely on the racial composition of the risk set.

CHAPTER 5

Ambient air pollution and preterm birth in Atlanta, 1994-2004: a time-series analysis

[Formatted for *Epidemiology*]

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ABSTRACT

Background: An emerging body of evidence suggests that ambient levels of air pollution during pregnancy may increase the risk of preterm birth. **Methods:** To further investigate these relationships we used vital record data to construct a retrospective cohort of 476,489 births occurring between 1994 and 2004 in five central counties of metropolitan Atlanta. Using a time-series approach, we examined aggregated daily counts of preterm birth in relation to ambient levels of carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone, PM_{10}, $PM_{2.5}$ and speciated PM measurements. Daily pollutant levels in five-county Atlanta were characterized using a population-weighted spatial average of air quality monitors in the study area. We also examined ambient concentrations at individual monitors in analyses limited to mothers with residential geocodes within four miles of each station. Relationships between average pollution levels in the first month of gestation, the week before birth and the six weeks before birth were modeled using Poisson generalized linear models. Results were adjusted for seasonal and long-term time trends. **Results:** Although we observed a predominance of null results, three positive associations between ambient pollution levels and preterm birth were observed in the four-mile capture area analyses. Preterm birth was associated with NO_2 in the six weeks before birth, $PM_{2.5}$ sulfate in the week before birth, and $PM_{2.5}$ water-soluble metals in the week before birth. **Conclusions:** Results provide some support for late pregnancy effects of ambient air pollution on preterm birth but should be interpreted with caution given the number of gestational windows and pollutants investigated.

INTRODUCTION

Preterm birth is a leading cause of infant morbidity and mortality, affecting 12.7% of births in the United States in 2005.[1] The specific etiologic pathways leading to preterm birth are poorly understood, and there is a recognized need to identify risk factors for this common pregnancy outcome.[2] An emerging body of evidence suggests that ambient levels of air pollution may play a role in the incidence of preterm birth.[3-5] However, the gestational window of susceptibility has not always been consistent across studies, with associations most commonly reported for exposures in early pregnancy (the first month or first trimester)[6-10] or in late pregnancy (the third trimester, the last 6 weeks, the last month, the last week).[6,8,9,11-15] Previous studies have also been inconsistent with regard to the specific pollutants associated with preterm birth; however, the majority of studies have observed associations with ambient measures of particulate matter (PM).[6-9,12-15] Sulfur dioxide (SO_2) as well as traffic related pollutants such as nitrogen dioxide (NO_2) and carbon monoxide (CO) have also been associated with preterm birth in a number of studies, but with less consistency.[6,9-17]

Although the pathophysiology of preterm birth remains poorly understood, evidence suggests a role for both inflammatory pathways as well as implantation errors in early pregnancy.[2] Both of these pathways offer plausible mechanisms by which air pollution could increase the risk of preterm birth. Air pollution levels in the weeks following conception could disrupt implantation and placentation and increase the risk of preterm birth through suboptimal placental function. In the final weeks of pregnancy, exposure to high levels of air pollution could activate an inflammatory response, either acute or sustained, leading to the initiation of early labor.

To investigate the relationship between ambient air pollution during gestation and the incidence of preterm birth, we conducted a time-series analysis in the central five-county area of metropolitan Atlanta over the period 1994-2004. We examined all US Environmental Protection Agency (EPA) criteria pollutants (O_3, SO_2, NO_2, CO, PM_{10}, $PM_{2.5}$), as well as speciated particle

measurements which are rarely available and have not been previously assessed in relation to preterm birth. We focused on three gestational windows of interest based on previous air pollution studies as well as current hypotheses about the biological mechanisms leading to preterm birth: the first month of gestation, the final week of gestation and the final six weeks of gestation. Our objective was to assess whether changes in ambient pollution levels during selected gestational windows are associated with changes in the rates of preterm birth.

METHODS

Study Population

We obtained Georgia vital record data for births to mothers residing in the five central counties of the Atlanta metropolitan area, Cobb, Clayton, DeKalb, Fulton and Gwinnett, from the Office of Health Research and Policy, Georgia Division of Public Health. The study area, shown in Figure 5.1, included 1752 square miles (4538 km^2), an area with a radius 16 miles (25.7 km) at its narrowest and 32 miles (51.5 km) at its widest. The cohort included singleton births who reached at least 20 weeks of gestation between January 1, 1994 and December 31, 2004 without major structural birth defects. We further restricted inclusion to Hispanic, non-Hispanic black, non-Hispanic white, or Asian infants with complete data on maternal marital status and education. After exclusions, 476,489 out of 509,776 births (93.5%) in the five-county area between January 1, 1994 and December 31, 2004 were eligible for analysis. There were 387,123 eligible births after January 1, 1996, when daily PM_{10} monitoring data began and there were 293,688 eligible births after August 1, 1998, when $PM_{2.5}$ and speciated PM monitoring began.

Outcome definition

Preterm birth was defined as live birth before 37 completed weeks of gestation; the earliest live births were recorded at 20 weeks gestation. For 98.5% of the cohort, gestational age was calculated using the reported date of the last menstrual period (LMP). For the remaining

1.5% of births, LMP date was missing or yielded an implausible gestational age of <20 or >44 weeks. The clinical estimate of gestational age was substituted for most of these (1.4% of births). For the remaining 0.1% of records without a valid LMP date or clinical estimate, we used the imputed gestational age provided by the Georgia Division of Public Health which was based on the birth weight of the infant. Our primary analysis included both spontaneous and induced preterm births. Because medically indicated preterm birth and spontaneous preterm birth share many of the same risk factors, we did not exclude preterm births due to medical intervention in our primary analysis.[18,19] However, we did conduct sensitivity analyses limited to spontaneous preterm births to assess the robustness of results.

The outcome definition differed slightly depending on the air pollution exposure window being investigated. For the late pregnancy windows, one week and six weeks prior to birth, the population was limited to infants who reached at least 29 weeks gestation; thus, preterm birth was defined as birth between 29 and 36 weeks. This was based on our *a priori* hypothesis that the acute effects of air pollution would be unlikely to induce extreme preterm birth between 20 and 28 weeks. In the first month of gestation exposure window, all preterm births between 20 and 36 weeks were included based on the hypothesis that disruption of the implantation and placentation process early in pregnancy could increase vulnerability to both extreme and moderate preterm birth.

Counts of preterm birth were determined for each day, either by conception date or birth date depending on how the air pollution window was defined. The daily counts of preterm birth (numerator) were offset by the number of pregnancies at risk each day (denominator). Calculation of the pregnancy risk set also differed by exposure window and is described in detail below.

Ambient Air Quality Data

We obtained ambient air pollution levels from three sources: 1) the U.S. EPA Air Quality System, 2) the Georgia Institute of Technology $PM_{2.5}$ network, and 3) the Aerosol

Research and Inhalation Epidemiology Study (ARIES) monitor located in downtown Atlanta. The daily air metrics obtained included 1-hour maximum carbon monoxide (CO), 1-hour maximum nitrogen dioxide (NO_2), 1-hour maximum sulfur dioxide (SO_2), 8- hour maximum ozone (O_3), and 24-hour average PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ components. Gaseous pollutants were available for the entire study period. Daily PM_{10} monitoring began in January 1996 and $PM_{2.5}$ and PM component monitoring began in August 1998. Monitoring instrumentation and methods used are described in Table 5.5.

For CO, NO_2, SO_2, O_3, PM_{10} and $PM_{2.5}$, we calculated a population-weighted spatial average for each day in the study area using methods described by Wade and colleagues (see section 5.14).[20] This approach took advantage of all the monitoring data available for each pollutant on a given day and yielded a daily spatial composite metric robust to missing data at individual monitoring sites.[20] In addition, it yielded a population-weighted average which may better approximate average population exposures than an unweighted average. There were five CO monitors, six NO_2 monitors, five SO_2 monitors, five O_3 monitors, nine PM_{10} monitors and eleven $PM_{2.5}$ monitors used to calculate the daily spatial averages. For the particle component measurements, $PM_{2.5-10}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ nitrate, $PM_{2.5}$ organic carbon, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ total carbon, and $PM_{2.5}$ water-soluble metals, daily measurements from the centrally located ARIES monitor were used. Ozone measurements were missing for six winter months between 1994 and 1996, when ozone levels are consistently low. We imputed these missing ozone values using results from a model in which temperature and week of year predicted the nonmissing ozone values. Ozone values calculated using this imputation strategy were highly correlated with measured ozone values in winters after 1996 when ozone was monitored ($r=0.79$ for one-week averages).

Exposure Assignment

To create the exposure assignment for each study date in the time-series analysis we averaged each daily pollutant value over the exposure window of interest. For the end of pregnancy exposure windows, air pollution assigned to each day represents the average pollution levels in the six weeks leading up to the study day, or the one week leading up to the study day. For the one month window, for which we analyze preterm counts by conception date, each study day is assigned the average pollution level in the following 28 days. For all pollutants and gestational windows of interest, an exposure was assigned only when at least 85% of days in the averaging window had available pollution data; otherwise the exposure assignment was set to missing, with the exception of imputed winter ozone values described above.

In a complementary approach, instead of using the five-county population-weighted spatial average for each pollutant, we created spatial capture areas around each monitor and conducted monitor-specific time-series analyses for the cohort of births with residential geocodes within four miles of the station. This approach allowed for the possibility that ambient measurements close to the maternal residential address might better correlate with personal exposures, particularly for primary pollutants which are more spatially heterogeneous (e.g., SO_2, CO, NO_2). For some pollutants, the four-mile buffers around monitoring stations overlapped; in such cases, maternal addresses within four miles of more than one station were assigned to the closest monitor. The capture areas were identical throughout the study period, but as a result of the overlap, were not necessarily perfect circles. We limited these monitor-specific analyses to monitors that recorded daily pollutant concentrations. Thus, several $PM_{2.5}$ and PM_{10} monitors which recorded levels every three or six days could not be included in this approach. As in the five-county analysis, an exposure was assigned only when at least 85% of the daily measurements in the exposure window were available.

Analytic approach

Daily counts of preterm birth were analyzed using Poisson generalized linear models. Pollutants were examined as continuous variables in single-pollutant models, using scaled variance estimates to account for overdispersion. In the spatial capture area approach, separate time-series analyses were run for the area surrounding each monitor, and effect estimates were pooled using inverse-variance weights to obtain a summary risk ratio for each pollutant.

Because ambient air pollution levels exhibit strong seasonal variation, and the incidence of preterm birth may also vary by season, we smoothly controlled for seasonal trends using parametric cubic splines.[21] We constrained the seasonal spline parameters in the model to be the same across all study years by including a day of year spline (day=1 to 365) with 12 monthly knots. In our descriptive analyses we observed racial, educational and marital status differences in the seasonality of birth; seasonal patterns of birth were similar across maternal age groups and parity. For example, births in the spring were more likely to be to mothers who were white, college-educated and married (see Chapter 4). Because these socio-demographic factors are related to the risk of preterm birth, we accounted for these seasonal trends explicitly by modeling temporal associations within racial (African American, white, Hispanic, Asian), educational (<12 years, 12-15 years, 16+ years) and marital status (married, unmarried) groups. Thus, each study day had multiple observations representing the counts of preterm birth within racial, educational and marital status strata. Accounting for these subtle trends directly allowed the day of year spline to adjust for other seasonal influences on the risk of preterm birth. We also smoothly adjusted for long-term temporal trends in preterm birth using a second cubic spline with knots on June 30th of each year.

Final one week and six weeks of gestation exposure windows

To examine pollution levels in the weeks preceding birth, preterm births were aggregated by birth date and offset by the number of ongoing gestations *in utero* at risk of preterm birth on

that day. Using this approach, a fetus enters the risk set at exactly 29 weeks gestation and exits the risk set either on the date of preterm birth or at 37 completed weeks of gestation, when they cease to be eligible for the outcome. Thus the risk set changes day to day. In our data, we observed seasonal differences in the gestational age distribution of the risk set due to the seasonality of birth in the study population. Because a risk set more heavily weighted toward later gestations (i.e., 35-36 weeks) would naturally experience a higher rate of preterm birth, we subdivided the risk set by gestational week and calculated daily counts of preterm birth within each gestational week, offsetting by the number of ongoing gestations at each specific gestational week. The models took the following form:

$$\log[E(Y_{t,w,r,k,m})] = \text{offset}_{t,w,r,k,m} + \alpha + \beta(\text{pollutant}_t) + \Sigma_{i=1\text{-}14}(\delta_i)(\text{long-term cubic spline}_t) + \Sigma_{j=1\text{-}15}(\gamma_j)(\text{seasonal cubic spline}_t) + \zeta(\text{weekend}) + \Sigma_{n=1\text{-}3}(\chi_n)(\text{race}_r) + \Sigma_{q=1\text{-}2}(\phi_q)(\text{education}_k) + \pi(\text{marital status}) + \Sigma_{v=29\text{-}36}(\varphi_v)(\text{gestational week}_w) + \Sigma_{x=1\text{-}24}(\tau_x)(\text{gestational week}_w * \text{race}_r) + \Sigma_{y=1\text{-}16}(\mu_y)(\text{gestational week}_w * \text{education}_k) + \Sigma_{z=1\text{-}8}(\psi_z)(\text{gestational week}_w * \text{marital status})$$

where $Y_{t,w,r,k,m}$ represents the number of preterm births on day *t*, at gestational week *w*, within stratum of race (African American, white, Hispanic, Asian), education (<12 years, 12-15 years, 16+ years), and marital status (married, unmarried). The offset, or denominator, is the number of ongoing pregnancies on day *t*, at gestational week *w* within strata of race (*r*), education (*k*) and marital status (*m*). The pollutant concentration represents the average concentration in the Atlanta area over the previous six weeks, or the average concentration over the past seven days. The product terms allow for possible interaction between the socio-demographic variables (race, education and marital status) and gestational age because the risk of preterm birth at various gestational weeks differed by these factors in our dataset and in the literature.[2] Although weekend status is not associated with weekly pollution averages, and therefore is not a potential confounder, we included it in the model to improve precision because it was a strong temporal

predictor of the outcome, particularly for the subset of induced preterm births. Based on our hypothesis that exposures near the end of pregnancy would be unlikely to induce an extremely preterm birth, we limited this analysis to preterm births occurring between 29 and 36 completed weeks of gestation. However, in a sensitivity analysis, we also examined extremely preterm births (births before 29 weeks) and calculated gestational week-specific risk ratios to explore the possibility that the effect of air pollution varies by degree of prematurity.

First-month-of-gestation exposure window

To examine pollution levels during the first month of gestation, births were aggregated by conception date, assumed to be 14 days after the LMP date, and each conception date was assigned the average pollution over the subsequent four weeks. Models took the form:

$$\log[E(Y_{t,r,k,m})] = \text{offset}_{t,r,k,m} + \alpha + \beta(\text{pollutant}_t) + \Sigma_{i=1\text{-}14}(\delta_i)(\text{long-term cubic spline}_t) + \Sigma_{j=1\text{-}15}(\gamma_j)(\text{seasonal cubic spline}_t) + \Sigma_{n=1\text{-}3}(\chi_n)(\text{race}_r) + \Sigma_{q=1\text{-}2}(\phi_q)(\text{education}_k) + \pi(\text{marital status}_m)$$

where $Y_{t,r,k,m}$ represents the number of conceptions on day *t* within strata of race (*r*), education (*k*) and marital status (*m*) who were eventually born preterm. The count was offset by the total number of conceptions on day *t* within the same racial, educational and marital strata. The count of preterm births between 20 and 36 weeks gestation of babies conceived on a given date was the dependent variable used to evaluate the hypothesis that disruption of the implantation and placentation process early in pregnancy could render the fetus more vulnerable to both extreme and moderate preterm birth.

For all exposure windows we conducted sensitivity analyses evaluating the robustness of results to more and less stringent control for long-term and seasonal trends, control for temperature and dew point over the exposure window of interest, and use of a central monitor instead of a population-weighted spatial average to assign exposure. We conducted stratified

analyses by season, year and socio-demographic factors such as race and maternal education to observe the consistency of results across these factors. All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Maternal and infant characteristics of the five-county cohort and the cohort of births within four miles of a monitor are displayed in Table 5.1. Relative to the five-county cohort, the cohort of births within four miles of a monitor had a higher percentage of preterm births (11.7% vs. 10.3%), were more likely to be African American (57% vs. 40%), less likely to be married (50% vs. 65%) and had fewer years of education (mean of 12.6 years vs. 13.2 years). On average, there were 12.2 preterm births per day, leading to 48,843 (10.3%) total preterm births over the entire study period.

Descriptive statistics of the five-county pollutant averages for each exposure window are presented in Table 5.2. Included in the table is the number of observation days used in each analysis, which differed by air quality data availability and the time-period for which all fetuses at risk could be identified (i.e., without birth data from 2005, the gestations at risk in late 2004 could not be fully identified). Correlations between the pollutant averages in each exposure window as well as descriptive statistics of daily pollutant levels are available in tables 5.7-5.9. Very few days were excluded in the five-county analysis based on the minimum 85% completeness criteria for CO (0%), NO_2 (0%), SO_2 (3%), O_3 (0%), PM_{10} (3%) and $PM_{2.5}$ (0%). For the speciated PM components limited to the ARIES monitoring station, a larger percentage of exposure assignments were excluded based on the 85% completeness criteria: $PM_{2.5\text{-}10}$ (19%), $PM_{2.5}$ sulfate (28%), $PM_{2.5}$ nitrate (28%), $PM_{2.5}$ total carbon (4%), $PM_{2.5}$ elemental carbon (4%), and $PM_{2.5}$ organic carbon (4%), and $PM_{2.5}$ water-soluble metals (28%). The percentage missing data reported above corresponds to the six-week exposure window; the one-week and four-week exposure windows had similar degrees of missing exposure assignments.

Five-county analysis

Risk ratios and 95% confidence intervals for the five-county analysis are presented in Table 5.3. Risk ratio estimates correspond to the relative increase in risk for one IQR increase in window-specific pollutant levels (IQRs shown in Table 5.2). Results were generally consistent with little or no association, although we observed negative associations between preterm birth and SO_2 in the first month of gestation and $PM_{2.5}$ sulfate in the last six weeks of gestation. Over the study period, there was a long-term decreasing trend in pollution levels and slight increase in preterm birth rates. Our main analysis controlled for these long-term trends using cubic splines with one knot per year; we did not find evidence for residual confounding by these long-terms trends in sensitivity analyses utilizing more and less stringent temporal control. In the season-stratified analyses, the negative associations between preterm birth and SO_2 during the first month and $PM_{2.5}$ sulfate during the last 6 weeks were not consistent across seasons (see Appendix B). Other sensitivity analyses did not meaningfully change the results. Stratification by race, maternal education and marital status did not suggest effect modification by these variables (Tables 5.10-5.12).

Capture area analysis

Risk ratios and 95% confidence intervals for the population of pregnancies within four miles of a monitor are presented in Table 5.4. Overall effect estimates reported for each pollutant were obtained using an inverse-variance weighted average of the effect estimates at each monitor and are scaled to the same IQR values used in the five-county analysis. The number of monitor-specific analyses included in the overall estimate calculation and the number of births captured by the four-mile buffers for each pollutant are also shown in Table 5.4. Observed effect estimates at each monitor for all pollutants and exposure windows are available in Table 5.13. We observed a positive association between preterm birth and $PM_{2.5}$ sulfate in the final week of gestation

(RR=1.09, 95% CI: 1.01–1.19, p=0.03), $PM_{2.5}$ water-soluble metals in the final week of gestation (RR=1.11, 95% CI: 1.02-1.22, p=0.02) and NO_2 in the final 6 weeks of gestation (RR=1.06, 95% CI: 1.02-1.09, p=0.001). The four monitor-specific results pooled in the overall NO_2 effect estimate for the six-week window are shown in Figure 5.2. For a 5 ppb increase in NO_2 in the six weeks before birth, estimated risk ratios were 1.06 (95% CI: 1.00-1.12, p=0.04) at the Georgia Tech monitor, 1.02 (95% CI: 0.92-1.13, p=0.74) at the ARIES Jefferson St. monitor, 1.06 (95% CI: 0.99-1.12, p=0.08) at the South DeKalb monitor and 1.07 (95% CI: 1.00-1.15, p=0.06) at the Tucker monitor. The wider confidence intervals at the ARIES monitor reflect the shorter monitoring period at that site. The observed associations for $PM_{2.5}$ sulfate and $PM_{2.5}$ water-soluble metals in the final week of gestation reflect associations solely at the ARIES monitor because no other monitors in our study area measured $PM_{2.5}$ components.

DISCUSSION

In this time-series analysis, we investigated the relationship between 13 ambient air pollutants during three gestational windows and the incidence of preterm birth. Most of the 78 relationships examined were consistent with little or no association between ambient air pollution and preterm birth. However, three air pollutants were associated with higher risk in the capture area approach: NO_2 in the six weeks before birth, $PM_{2.5}$ sulfate in week before birth and $PM_{2.5}$ water-soluble metals in the week before birth. Two pollutants were associated with lower risk in the larger five-county analysis: SO_2 in the first month of gestation and $PM_{2.5}$ sulfate in the six weeks before birth.

Our two approaches to exposure assignment have relative strengths and weaknesses, and one of the two approaches may be preferable for a given pollutant and gestational window. The finer spatial scale of exposure assignment provided by the capture area approach may have better approximated exposures for mothers living near the monitor, particularly for CO, NO_2, SO_2, $PM_{2.5}$ elemental carbon, and $PM_{2.5}$ organic carbon, which are primary pollutants.[22] Although this

approach is intuitively appealing, it is unclear whether the closest monitor better approximates personal exposures when compared to a city-wide metric.[23,24] Pregnant women may spend a large portion of their day away from their residence, and with previous studies showing that 20% of women in Atlanta change residences during pregnancy, exposure assignment based on the residence at time of birth is problematic for assessment of early gestational windows.[25,26] Furthermore, individual monitors are sited for different purposes, and measured levels may not represent concentrations beyond the immediate vicinity of the monitor. For spatially homogenous pollutants such as O_3 and $PM_{2.5}$ sulfate, for which monitors in the study area have strong longitudinal correlations, the five-county population-weighted average may provide a better measure of population average exposure while permitting analysis of the entire birth cohort.

Conflicting results from the two approaches may also reflect differences in population susceptibility. Notably, mothers residing near a monitor were more likely to be black, less educated, unmarried and were at an overall higher risk of preterm birth. Increased sensitivity to the adverse effects of air pollution in lower SES groups, for example, could be explained by a lack of access to health care, nutritional deficiencies[27], or concurrent exposure to other occupational and environmental hazards. Effect modification by SES-related characteristics could also act indirectly through better exposure assessment in these individuals; lower SES groups may be more exposed to ambient air because of less access to air conditioning, greater infiltration of ambient pollutants into older, inner city housing,[28] and occupations or daily activity patterns which involve more time spent outdoors. However, when we stratified the five-county population by available SES-related variables, such as race, maternal education and marital status, the results did not suggest effect modification by these variables.

In the five-county analysis we observed inverse associations with first-month SO_2 and $PM_{2.5}$ sulfate in the last six weeks of pregnancy, although the upper confidence limits for both associations were close to 1.00. Sulfur dioxide concentrations in Atlanta are extremely spatially heterogeneous, driven by point-source plume touchdowns from local coal-fired power plants and

a coal-fired cement facility.[22] We have little confidence in the five-county analysis results for SO_2. Chance is a potential explanation for any of the associations observed in this study, given the number of comparisons made.

One of the positive associations observed in the capture area but not the five-county approach was for $PM_{2.5}$ sulfate, one of the most spatially homogeneous pollutants in the dataset.[22] As a secondary pollutant without indoor sources, personal-ambient correlations for $PM_{2.5}$ sulfate have been shown to be very high when using a city-wide exposure measure (median r^2=0.96).[23] Although we were only able to assess $PM_{2.5}$ sulfate around one monitor (ARIES), total $PM_{2.5}$ is strongly correlated with $PM_{2.5}$ sulfate (r=0.84 for one-week averages) and was monitored at six stations. Like $PM_{2.5}$ sulfate, the risk ratio for $PM_{2.5}$ at the ARIES monitor was elevated at 1.06 (95% CI: 0.98-1.14), but when combined into a pooled estimate across the six $PM_{2.5}$ monitors, the risk ratio for the final week of gestation was 1.00 (0.96–1.03). This suggests that the $PM_{2.5}$ sulfate association may not have been consistent across other monitoring sites. In contrast, $PM_{2.5}$ water-soluble metals are more spatially heterogeneous, and it is possible that the capture area approach detected an association that was washed out by measurement error in the five-county analysis. However, in light of the number of associations examined, the limitation of measurements to one monitoring station, and the fact that these $PM_{2.5}$ constituents have not been previously assessed in relation to preterm birth, these associations warrant cautious interpretation and should be examined in other populations.

The positive association between NO_2 in the final six weeks of pregnancy and preterm birth is perhaps more compelling. The consistency of the effect estimates observed across the four individual NO_2 monitors adds strength to the evidence of an association, and the spatial heterogeneity of this primary pollutant could explain why an association was not observed in the five-county analysis. However, previous studies investigating NO_2 in late pregnancy have yielded mixed results. Associations between preterm birth and ambient levels of NO_2 in late pregnancy have been observed in the Czech Republic and Korea, but not in Los Angeles, Sydney, or

Brisbane.[6,7,9,12,16] In Vancouver, the association between NO_2 in the last four weeks of gestation and preterm birth was suggestive (RR= 1.08 ; 95% CI: 0.99–1.17 per 10 ppb increase).[11] As in any study of ambient air pollution, the specific pollutants examined may serve as surrogates for other unmeasured, or less well measured, pollutants. Several studies have observed associations between preterm birth and traffic sources or traffic-related pollutants other than NO_2.[8,9,11,12,14,17] It is possible that in our study setting, using a spatial resolution of four miles around each monitor, NO_2 levels act as a surrogate of traffic-related pollution. In contrast to previous reports, we did not observe associations between preterm birth and CO, $PM_{2.5}$, PM_{10}, SO_2 or O_3.

The majority of previous studies have utilized spatio-temporal contrasts of exposure, comparing pregnant women across both space and time. Residual confounding by spatially varying individual risk factors such as socioeconomic status, which can be difficult to quantify and adequately control, is a concern in these studies.[29] To reduce the plausibility of confounding by individual level risk factors, we conducted a temporal analysis in which comparisons were made across days instead of individuals. Furthermore, we were able to incorporate finer spatial resolution of ambient air pollution concentrations using population capture areas around each monitor, while still maintaining the purely temporal nature of the analysis. Other strengths of our study include a study cohort of nearly 500,000 births, and the assessment of rarely available air quality measurements that investigators have speculated may be driving associations previously reported in the literature.

One possible explanation for some of the null results could be an underestimation of effects due to the use of ambient measurements instead of actual personal exposures. To reduce this bias toward the null in a time-series setting, measured ambient levels should be strongly longitudinally correlated with the *average* personal exposure in the study population.[30,31] By using a population-weighted spatial average in the five-county analysis and conducting capture area analyses at a finer spatial scale, we attempted to mitigate this issue. Nonetheless, for

pollutants with fine-scale spatial heterogeneity, bias toward the null may have obscured any true effects.

Although we considered and accounted for several potential temporal confounders, it is possible our results are confounded by some unknown temporally varying risk factor. It is worth noting that these same unknown temporal confounders would also be of concern in studies using a spatio-temporal approach, although their effect might be different across sites. In addition to exposure measurement error, gestational age is undoubtedly misclassified on many birth records in our study.[32] The degree and direction of misclassification, however, is likely to be independent of air pollution, and the reduction of power resulting from outcome misclassification was mitigated by our large sample size. A limitation of examining early gestational windows is the inability to identify all conceptions; in our study we could only identify conceptions who survived to 20 weeks and delivered within the state of Georgia. If early pregnancy exposure to air pollution increases the risk of fetal loss in addition to preterm birth, associations between air pollution and preterm birth would be underestimated. Other limitations of our study include possible misspecification of the gestational window of vulnerability and the issue of multiple comparisons.

In summary, we observed some evidence of an effect for NO_2, $PM_{2.5}$ sulfate and $PM_{2.5}$ water-soluble metals on the risk of preterm birth. However, these findings should be interpreted with caution in light of our comprehensive approach to data analysis that included investigating multiple pollutants over multiple gestational windows and lack of strong *a priori* evidence for an effect of these pollutants. Observed effect sizes were small, but may have been attenuated by exposure measurement error. Nonetheless, because small increases in risk associated with a ubiquitous exposure could have large public health impacts, future studies of the possible association of air pollution with preterm birth are warranted. Future studies, including toxicological experiments, personal-ambient correlation studies of pregnant women, and studies utilizing more detailed exposure modeling may help to refine evolving hypotheses about the relationship between ambient air pollution and preterm birth.

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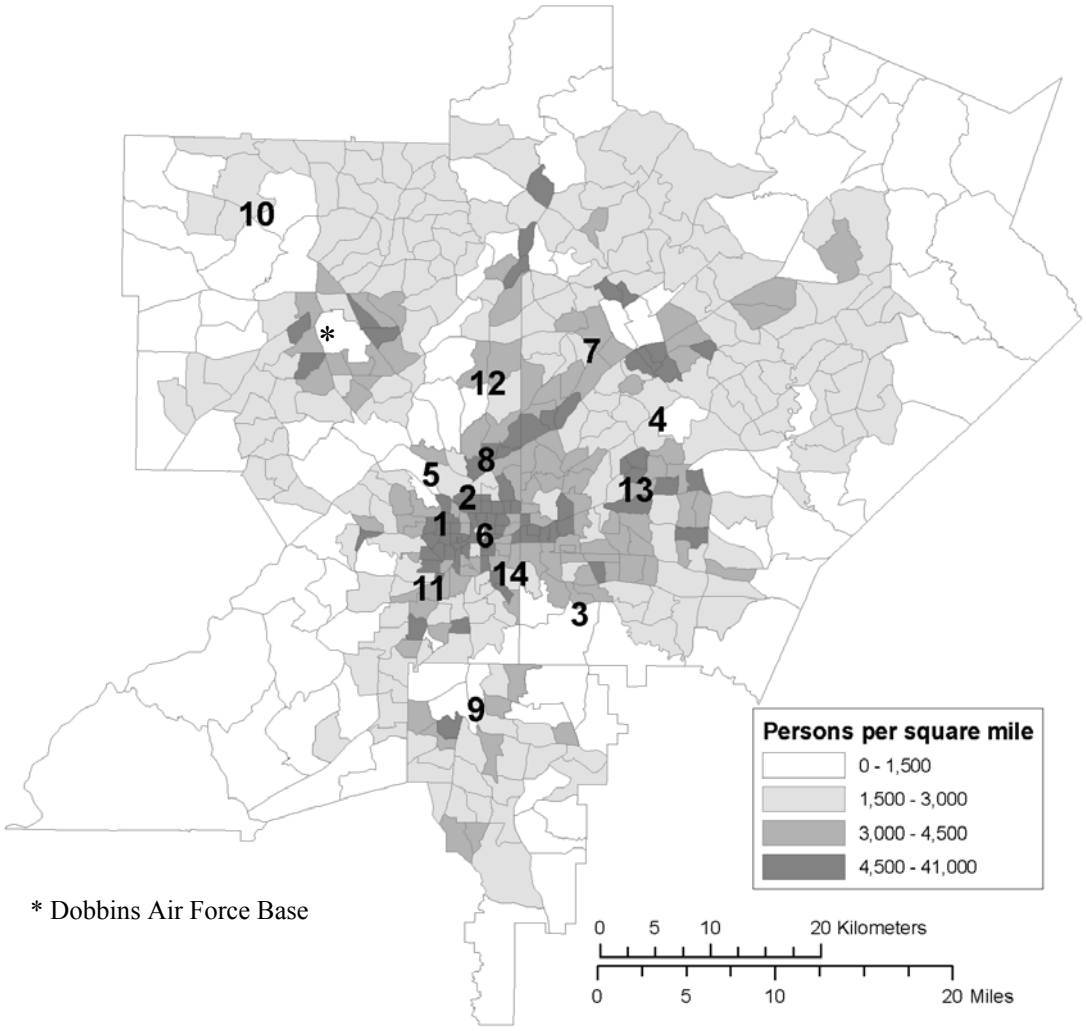

Figure 5.1. Five-county Atlanta study area, population density and location of ambient air quality monitoring stations

1. Jefferson St: CO, NO_2, SO_2, O_3, PM_{10}, $PM_{2.5}$, PM components	
2. Georgia Tech: NO_2, SO_2, PM_{10}	
3. South DeKalb: NO_2, O_3, $PM_{2.5}$	**9**. Forest Park: $PM_{2.5}$
4. Tucker: NO_2, $PM_{2.5}$	**10.** Kennesaw: $PM_{2.5}$
5. Fire Station 8: $PM_{10,}$ $PM_{2.5}$	**11.** Fort McPherson: $PM_{2.5}$
6. Fulton Health Dept: PM_{10}	**12.** Roswell Road: CO
7. Doraville Health Center: $PM_{10,}$ $PM_{2.5}$	**13.** DeKalb Tech: CO
8. East Rivers School: $PM_{10,}$ $PM_{2.5}$	**14.** Confederate Ave: SO_2, O_3

Table 5.1. Maternal and infant characteristics for births in five-county Atlanta January 1, 1994- December 31, 2004, and for births within four miles of a monitoring station included in the capture area analysis.

	Five-county Atlanta (N=476,489)* Number (%)	Births within 4 miles of a monitor (N=136,858)* Number (%)
Preterm birth	48,843 (10.3)	15,946 (11.7)
Female	233,931 (49.1%)	67,313 (49.2)
Maternal age group (years)		
<20	49,359 (10.4)	19,419 (14.2)
20-34	355,515 (74.6)	99,135 (72.4)
35+	71,615 (15.0)	18,304 (13.4)
Maternal race		
white	199,717 (41.9)	33,504 (24.5)
African American	190,781 (40.0)	78,094 (57.1)
Hispanic	63,347 (13.3)	19,749 (14.4)
Asian	22,644 (4.8)	5,511 (4.0)
Maternal Education (completed years)		
<12	92514 (19.4)	36794 (26.9)
12-15	223,409 (46.9)	63,216 (46.2)
16+	160,566 (33.7)	36,848 (26.9)
Married	307,996 (64.6)	68,411 (50.0)
First birth	208,526 (43.8)	60,317 (44.1)
Reported tobacco use	23,041 (4.8)	6,457 (4.7)
Season of birth		
Winter (December-February)	116,601 (24.5)	33,530 (24.5)
Spring (March-May)	117,642 (25.7)	33,446 (24.4)
Summer (June-August)	121,945 (25.6)	34,732 (25.4)
Fall (September-November)	120,301 (25.3)	35,150 (25.7)
Year of birth		
1994	37,899 (8.0)	8,757 (6.4)
1995	38,288 (8.0)	9,964 (7.3)
1996	38,744 (8.1)	10,552 (7.7)
1997	40,463 (8.5)	10,724 (7.8)
1998	41,508 (8.7)	11,059 (8.1)
1999	43,207 (9.1)	13,563 (9.9)
2000	46,375 (9.7)	15,217 (11.1)
2001	47,660 (10.0)	15,493 (11.3)
2002	47,288 (9.9)	14,927 (10.9)
2003	47,421 (10.0)	13,744 (10.0)
2004	47,636 (10.0)	12,858 (9.4)

*excludes plural births, major structural congenital birth defects, and missing race, education and marital status

Table 5.2. Descriptive statistics of pollution levels for each gestational window of exposure using the population weighted spatial composite pollutant values (gaseous pollutants, PM_{10} and $PM_{2.5}$) and the ARIES station measurements ($PM_{2.5\text{-}10}$ and $PM_{2.5}$ components).

POLLUTANT	4-week average ‡				1-week average §				6-week average §			
	N*	Mean ± SD	IQR**	Range	N*	Mean ± SD	IQR**	Range	N*	Mean ± SD	IQR**	Range
1-hour max carbon monoxide (ppm)	3806	0.93 ±0.22	0.32	0.52-1.70	3834	0.91 ±0.28	0.37	0.24-2.35	3834	0.91 ±0.20	0.30	0.51-1.47
1-hour max nitrogen dioxide (ppb)	3780	23.5 ±4.0	5	12.6-38.5	3827	23.5 ±6.0	8	8.0-46.1	3834	23.6 ±3.5	5	14.7-33.5
1-hour max sulfur dioxide (ppb)	3742	10.5 ±3.1	4	3.9-22.7	3802	10.3 ±4.7	6	1.4- 30.7	3736	10.3 ±2.6	3	4.2 -18.8
8-hour max ozone (ppb)	3806	44.1 ±15.0	25	18.7-90.1	3834	44.4 ±16.7	25	10.3-96.9	3834	44.3 ±14.4	25	20.0-85.0
24-hour PM_{10} ($\mu g/m^3$)	2916	23.9 ±6.3	8	10.8-51.8	3017	23.9 ±8.2	10	7.4 -68.7	2976	23.9 ±5.7	8	13.2-43.6
24-hour $PM_{2.5}$ ($\mu g/m^3$)	1994	16.5 ±4.0	5	9.8-34.1	2111	16.4 ±5.2	6	6.9- 41.9	2130	16.5 ±3.7	5	10.5-30.5
24-hour $PM_{2.5\text{-}10}$ ($\mu g/m^3$)	1734	9.1 ±2.5	2.7	4.6-19.2	1889	9.1 ±3.3	3.6	2.6-25.6	1731	9.1 ±2.2	2.5	4.9-16.7
24-hour $PM_{2.5}$ sulfate ($\mu g/m^3$)	1594	4.9 ±2.2	2.8	1.9-13.3	1782	4.8 ±2.5	3.0	1.1-15.6	1533	4.9 ±2.0	2.8	2.0-11.9
24-hour $PM_{2.5}$ nitrate ($\mu g/m^3$)	1591	0.98 ±0.49	0.66	0.30-2.67	1781	1.00 ±0.60	0.75	0.23-4.25	1531	0.94 ±0.46	0.64	0.31-3.55
24-hour $PM_{2.5}$ total carbon ($\mu g/m^3$)	1951	6.0 ±1.4	1.6	3.3-11.4	2007	5.9 ±2.0	2.3	2.2-15.4	2047	6.0 ±1.2	1.7	3.7- 10.2
24-hour $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	1951	1.63 ±0.52	0.53	0.78-4.31	2007	1.60 ±0.71	0.70	0.45-7.56	2047	1.63 ±0.49	0.55	0.96-3.61
24-hour $PM_{2.5}$ organic carbon ($\mu g/m^3$)	1951	4.4 ±1.0	1.2	2.4-8.3	2013	4.3 ±1.4	1.7	1.5-12.1	2047	4.4 ±0.8	1.2	2.6-7.4
24-hour $PM_{2.5}$ water-soluble metals † ($\mu g/m^3$)	1604	0.030 ±0.011	0.017	0.009-0.066	1789	0.029 ±0.015	0.020	0.005-0.104	1540	0.030 ±0.012	0.016	0.010-0.079

‡ Time period: gases 9/15/1993-2/15/2004 (3806 days), PM_{10} 1/1/1996-2/15/2004 (2968 days), $PM_{2.5}$ 9/1/1998-2/15/2004 (1994 days)
§ Time period: gases 1/1/94-6/30/2004 (3834 days), PM_{10} 2/1/1996-6/30/04 (3073 days), $PM_{2.5}$ 9/1/1998-6/30/2004 (2130 days)
* Number of days over time period with nonmissing pollution values
** Interquartile range (75^{th} percentile - 25^{th} percentile)
† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table 5.3. Risk ratios and 95% confidence intervals** for associations between air pollution levels in the three gestational windows of interest and preterm birth for births in five-county Atlanta

	Exposure Window		
	First month of gestation ¥ RR (95% CI)	Final week of gestation ‡ RR (95% CI)	Final 6 weeks of gestation ‡ RR (95% CI)
1-h max CO (ppm)	1.01 (0.99–1.04)	1.00 (0.98–1.02)	0.97 (0.94–1.01)
1-h max NO_2 (ppb)	0.99 (0.98–1.01)	1.00 (0.98–1.01)	1.00 (0.98–1.02)
1-h max SO_2 (ppb)	0.97 (0.96–0.99)*	0.99 (0.98–1.01)	0.99 (0.97–1.01)
8-h max O_3 (ppb)	0.96 (0.92–1.00)	0.99 (0.96–1.01)	1.00 (0.95–1.06)
24-h PM_{10} ($\mu g/m^3$)	0.99 (0.97–1.01)	0.99 (0.97–1.00)	0.98 (0.95–1.01)
24-h $PM_{2.5}$ ($\mu g/m^3$)	1.00 (0.98–1.03)	0.98 (0.97–1.00)	0.99 (0.95–1.02)
24-h $PM_{2.5-10}$ ($\mu g/m^3$)	1.00 (0.97–1.02)	0.99 (0.97–1.01)	1.01 (0.98–1.04)
24-h $PM_{2.5}$ sulfate ($\mu g/m^3$)	1.00 (0.97–1.03)	0.98 (0.96–1.01)	0.95 (0.90–1.00)*
24-h $PM_{2.5}$ nitrate ($\mu g/m^3$)	1.01 (0.97–1.05)	0.99 (0.96–1.01)	0.98 (0.93–1.04)
24-h $PM_{2.5}$ total carbon ($\mu g/m^3$)	0.99 (0.97 –1.01)	0.99 (0.97–1.01)	1.00 (0.97–1.03)
24-h $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	0.99 (0.97–1.02)	1.00 (0.98–1.02)	1.00 (0.97–1.04)
24-h $PM_{2.5}$ organic carbon ($\mu g/m^3$)	0.99 (0.97–1.01)	0.99 (0.97–1.00)	1.00 (0.97–1.02)
24-h $PM_{2.5}$ water-soluble metals† ($\mu g/m^3$)	1.01 (0.97–1.05)	0.98 (0.96–1.01)	0.96 (0.91–1.03)

* $p<0.05$

** Risk ratios and 95% confidence intervals correspond to an IQR increase in pollutant value for each exposure window reported in Table 5.2

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ Counts aggregated by conception date, offset by total conceptions, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education

‡ Counts aggregated by birth date, offset by gestations at risk, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

Table 5.4. Risk ratios and 95% confidence intervals** for associations between air pollution levels in the three gestational windows of interest and preterm birth for births with a maternal residential address within 4 miles of a monitor.

	Exposure Window			N monitors	N births within 4 miles of a monitor §
Pollutant	First month of gestation ¥ RR (95% CI)	Final week of gestation ‡ RR (95% CI)	Final 6 weeks of gestation ‡ RR (95% CI)		
1-hour max CO (ppm)	0.99 (0.95–1.02)	1.01 (0.99–1.03)	1.01 (0.97–1.06)	3	60,842
1-hour max NO_2 (ppb)	1.01 (0.99–1.04)	1.01 (0.98–1.04)	1.06 (1.02–1.09)*	4	68,801
1-hour max SO_2 (ppb)	1.00 (0.97–1.03)	0.99 (0.96–1.02)	0.98 (0.95–1.02)	3	45,974
8-hour max O_3 (ppb)	0.94 (0.83–1.05)	1.00 (0.94–1.08)	1.06 (0.91–1.24)	3	50,994
24-hour PM_{10} ($\mu g/m^3$)	1.07 (0.99–1.17)	1.06 (0.99–1.13)	1.01 (0.90–1.14)	2	27,469
24-hour $PM_{2.5}$ ($\mu g/m^3$)	0.99 (0.93–1.05)	1.00 (0.96–1.03)	1.05 (0.96–1.16)	6	68,643
24-hour $PM_{2.5-10}$ ($\mu g/m^3$)	1.03 (0.95–1.12)	1.03 (0.97–1.10)	1.07 (0.97–1.18)	1	17,086
24-hour $PM_{2.5}$ sulfate ($\mu g/m^3$)	1.06 (0.94–1.20)	1.09 (1.01–1.19)*	0.93 (0.77–1.11)	1	17,086
24-hour $PM_{2.5}$ nitrate ($\mu g/m^3$)	1.03 (0.89–1.20)	0.98 (0.90–1.08)	0.86 (0.71–1.04)	1	17,086
24-hour $PM_{2.5}$ total carbon ($\mu g/m^3$)	1.02 (0.95–1.09)	1.02 (0.96–1.09)	0.97 (0.88–1.08)	1	17,086
24-hour $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	1.01 (0.93–1.10)	1.04 (0.98–1.10)	0.97 (0.86–1.08)	1	17,086
24-hour $PM_{2.5}$ organic carbon ($\mu g/m^3$)	1.02 (0.94–1.10)	1.01 (0.95–1.08)	0.98 (0.89–1.07)	1	17,086
24-hour $PM_{2.5}$ water-soluble metals ($\mu g/m^3$) †	1.07 (0.93–1.24)	1.11 (1.02–1.22)*	0.89 (0.72–1.09)	1	17,086

* $p<0.05$

** Risk ratios and 95% confidence intervals correspond to an IQR increase in pollutant value for each exposure window reported in Table 5.2

§ Exact number of births analyzed differed slightly by exposure window and pollutant missingness

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ Counts aggregated by conception date, offset by total conceptions, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education

‡ Counts aggregated by birth date, offset by gestations at risk, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

Figure 5.2. Monitor-specific risk ratios and 95% confidence intervals for preterm birth for a 5 ppb increase in NO_2 levels in the final six weeks of gestation.

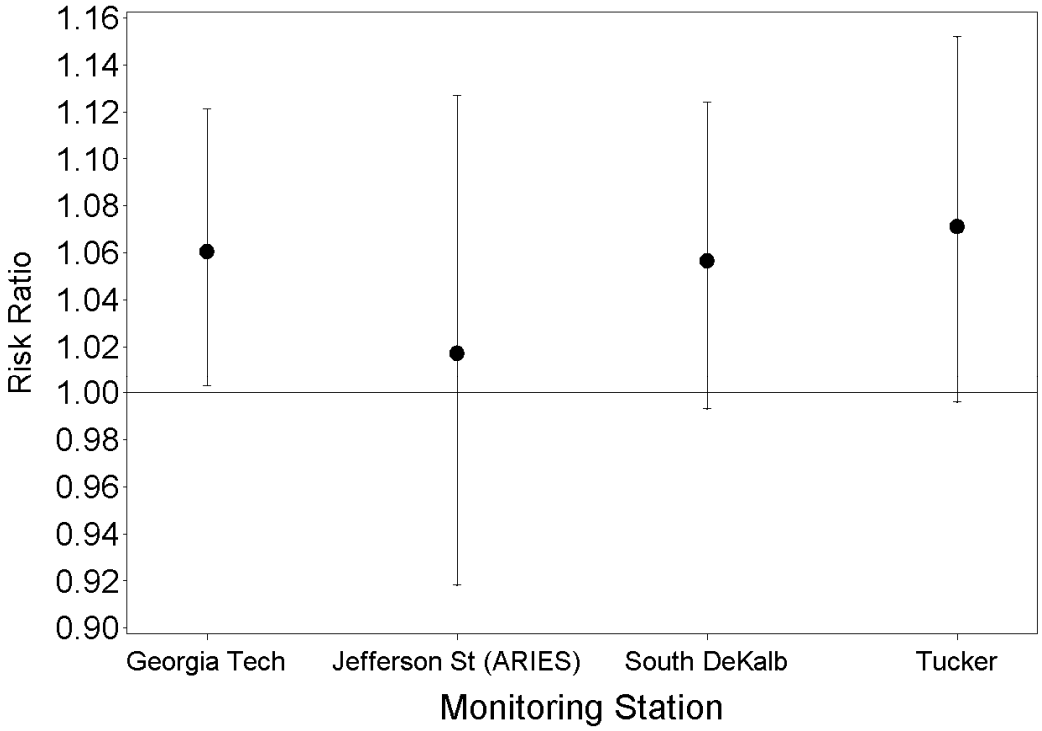

Table 5.5. Air quality monitoring instrumentation, network and frequency by station

AQ Variable	Site Location	Network	Method	Frequency
PM_{10}	Georgia Tech	AQS	TEOM	Daily
	Jefferson Street (ARIES)	SEARCH	FRM	Daily
	Yorkville	SEARCH	FRM	Daily
	Fulton Co. Health Dept.	AQS	FRM	Every 6th day
	Fire Station #8	AQS	FRM	Every 6th day
	Doraville Health Center	AQS	FRM	Every 6th day
	Griffin	AQS	FRM	Every 6th day
	Douglasville	AQS	FRM	Every 6th day
	E. Rivers School	AQS	FRM	Every 6th day
$PM_{2.5}$	Doraville Health Center	AQS	FRM	Daily
	East Rivers School	AQS	FRM	Daily
	South DeKalb	AQS/ASACA	FRM/TEOM	Daily
	Fort McPherson	ASACA	TEOM	Daily
	Tucker	ASACA	TEOM	Daily
	Jefferson Street (ARIES)	SEARCH	FRM	Daily
	Yorkville	SEARCH	FRM	Daily
	Fire Station #8	AQS	FRM	Every 3rd day
	East Point Health Center	AQS	FRM	Every 3rd day
	Forest Park	AQS	FRM	Every 3rd day
	Kennesaw	AQS	FRM	Every 3rd day
$PM_{2.5-10}$	Jefferson St. (ARIES)	SEARCH	Dichotomous Sampler	Daily
$PM_{2.5}$ sulfate	Jefferson St. (ARIES)	SEARCH	Particle Composition Monitor	Daily
$PM_{2.5}$ nitrate	Jefferson St. (ARIES)	SEARCH	Particle Composition Monitor	Daily
$PM_{2.5}$ TC	Jefferson St. (ARIES)	SEARCH	Thermal Optical Reflectance	Daily
$PM_{2.5}$ EC	Jefferson St. (ARIES)	SEARCH	Thermal Optical Reflectance	Daily
$PM_{2.5}$ OC	Jefferson St. (ARIES)	SEARCH	Thermal Optical Reflectance	Daily
$PM_{2.5}$ WS metals	Jefferson St. (ARIES)	SEARCH	Particle Composition Monitor	Daily
O_3	Confederate Ave.	AQS	Chemiluminescence	Missing winter
	South DeKalb	AQS	Chemiluminescence	Missing winter
	Conyers	AQS	Chemiluminescence	Missing winter
	Jefferson Street (ARIES)	SEARCH	UV Absorption	Daily
	Yorkville	SEARCH	UV Absorption	Daily
CO	DeKalb Tech	AQS	Infrared analyzer	Daily
	Roswell Rd.	AQS	Infrared analyzer	Daily
	South DeKalb	AQS	Infrared analyzer	Daily
	Jefferson Street (ARIES)	SEARCH	Infrared analyzer	Daily
	Yorkville	SEARCH	Infrared analyzer	Daily
SO_2	Confederate Ave.	AQS	Fluorescence	Daily
	Georgia Tech	AQS	Fluorescence	Daily
	Stilesboro	AQS	Fluorescence	Daily
	Jefferson Street (ARIES)	SEARCH	Fluorescence	Daily
	Yorkville	SEARCH	Fluorescence	Daily
NO_2	Georgia Tech	AQS	Chemiluminescence	Daily
	South DeKalb	AQS	Chemiluminescence	Daily
	Conyers	AQS	Chemiluminescence	Daily
	Tucker	AQS	Chemiluminescence	Daily
	Jefferson St. (ARIES)	SEARCH	Chemiluminescence	Daily
	Yorkville	SEARCH	Chemiluminescence	Daily

AQS = EPA Air Quality System ASACA= Assessment of Spatial Aerosol Composition in Atlanta SEARCH= Southeastern Aerosol Research and Characterization FRM = Federal Reference Method TEOM = Tapered Element Oscillating Microbalance

Table 5.6. Descriptive statistics of daily pollution levels for the five-county Atlanta metropolitan area using a population-weighted spatial average of available monitors.

		Daily Levels		
Pollutant	N*	Mean ± SD	IQR	Range
1-hour max carbon monoxide (ppm)	4017	0.89 ± 0.47	0.57	0.10-3.49
1-hour max nitrogen dioxide (ppb)	4015	23.4 ± 9.7	13	1.7-97.0
1-hour max sulfur dioxide (ppb)	4001	10.2 ± 8.9	10	0.4-78.1
8-hour max ozone (ppb)	4017	44.1 ± 19.9	29	1.2-114.5
24-hour PM_{10} ($\mu g/m^3$)	3239	23.8 ± 11.5	15	3.4-98.9
24-hour $PM_{2.5}$ ($\mu g/m^3$)	2338	16.4 ± 7.4	9	3.4-66.8
24-hour $PM_{2.5-10}$ ($\mu g/m^3$)	2183	9.0 ± 5.0	6	0.5-50.3
24-hour $PM_{2.5}$ sulfate ($\mu g/m^3$)	2135	4.9 ± 3.4	3.8	0.5-21.9
24-hour $PM_{2.5}$ nitrate ($\mu g/m^3$)	2127	1.00 ± 0.84	0.86	0.02-7.39
24-hour $PM_{2.5}$ total carbon ($\mu g/m^3$)	2258	6.0 ± 3.4	3.6	0.6-33.7
24-hour $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	2258	1.63 ± 1.15	1.15	0.05-11.89
24-hour $PM_{2.5}$ organic carbon ($\mu g/m^3$)	2259	4.4 ± 2.4	2.6	04.-25.9
24-hour $PM_{2.5}$ water-soluble metals † ($\mu g/m^3$)	2138	0.030 ± 0.023	0.025	0.003- 0.202

*Time period: Gases 1/1/94-12/31/04, PM_{10} 1/1/96-12/31/04, $PM_{2.5}$ and components 9/1/98-12/31/04

Table 5.7. Spearman correlation coefficients between four-week average pollutant concentrations in five-county Atlanta.

	CO	NO_2	SO_2	O_3	PM_{10}	$PM_{2.5}$	CP	SO_4	NO_3	TC	EC	OC	WSMET
N observations	3806	3780	3742	3806	2916	1994	1734	1594	1591	1951	1951	1951	1604
CO	1												
NO_2	0.36	1											
SO_2	0.44	0.37	1										
O_3	-0.29	0.00	-0.32	1									
PM_{10}	0.12	0.06	-0.17	0.78	1								
$PM_{2.5}$	0.07	0.05	-0.12	0.67	0.91	1							
CP ($PM_{2.5-10}$)	0.31	0.26	-0.17	0.48	0.71	0.53	1						
SO_4 ($PM_{2.5}$ sulfate)	-0.16	-0.15	-0.22	0.83	0.82	0.87	0.34	1					
NO_3 ($PM_{2.5}$ nitrate)	0.35	0.51	0.66	-0.68	-0.38	-0.26	-0.36	-0.52	1				
TC ($PM_{2.5}$ total carbon)	0.74	0.70	0.29	-0.09	0.45	0.39	0.36	0.04	0.24	1			
EC ($PM_{2.5}$ elemental carbon)	0.86	0.64	0.34	-0.10	0.41	0.41	0.42	0.11	0.18	0.86	1		
OC ($PM_{2.5}$ organic carbon)	0.59	0.66	0.24	-0.07	0.42	0.34	0.28	0.01	0.24	0.96	0.69	1	
WSMET ($PM_{2.5}$ WS metals)	-0.01	-0.15	-0.25	0.59	0.73	0.69	0.44	0.76	-0.53	0.12	0.25	0.05	1

Time period: gases 9/15/1993-2/15/2004 (3806 days), PM_{10} 1/1/1996-2/15/2004 (2968 days), $PM_{2.5}$ and components 9/1/1998-2/15/2004 (1994 days)

Table 5.8. Spearman correlation coefficients between one-week average pollutant concentrations in five-county Atlanta.

	CO	NO_2	SO_2	O_3	PM_{10}	$PM_{2.5}$	CP	SO_4	NO_3	TC	EC	OC	WSMET
N observations	3834	3827	3802	3834	3017	2111	1889	1782	1781	2007	2007	2013	1789
CO	1												
NO_2	0.49	1											
SO_2	0.27	0.42	1										
O_3	-0.08	0.22	-0.11	1									
PM_{10}	0.38	0.43	0.10	0.69	1								
$PM_{2.5}$	0.37	0.39	0.11	0.62	0.91	1							
CP ($PM_{2.5-10}$)	0.40	0.45	0.07	0.46	0.74	0.53	1						
SO_4 ($PM_{2.5}$ sulfate)	0.03	0.04	-0.07	0.73	0.77	0.84	0.33	1					
NO_3 ($PM_{2.5}$ nitrate)	0.27	0.34	0.38	-0.50	-0.12	0.01	-0.17	-0.26	1				
TC ($PM_{2.5}$ total carbon)	0.74	0.74	0.27	0.13	0.61	0.54	0.49	0.21	0.22	1			
EC ($PM_{2.5}$ elemental carbon)	0.82	0.66	0.33	0.08	0.54	0.52	0.47	0.23	0.20	0.87	1		
OC ($PM_{2.5}$ organic carbon)	0.62	0.70	0.22	0.14	0.58	0.51	0.45	0.17	0.21	0.97	0.72	1	
WSMET ($PM_{2.5}$ WS metals)	0.25	0.16	0.00	0.55	0.73	0.70	0.48	0.73	-0.27	0.36	0.42	0.29	1

Time period: gases 1/1/94-6/30/2004 (3834 days), PM_{10} 2/1/1996-6/30/04 (3073 days), $PM_{2.5}$ and components 9/1/1998-6/30/2004 (2130 days)

Table 5.9. Spearman correlation coefficients between six-week average pollutant concentrations in five-county Atlanta.

	CO	NO_2	SO_2	O_3	PM_{10}	$PM_{2.5}$	CP	SO_4	NO_3	TC	EC	OC	WSMET
N observations	3834	3834	3736	3834	2976	2130	1731	1533	1531	2047	2047	2047	1540
CO	1												
NO_2	0.31	1											
SO_2	0.42	0.34	1										
O_3	-0.33	-0.07	-0.39	1									
PM_{10}	0.16	0.10	-0.18	0.76	1								
$PM_{2.5}$	0.26	0.13	-0.05	0.68	0.91	1							
CP ($PM_{2.5-10}$)	0.30	0.23	-0.25	0.50	0.69	0.51	1						
SO_4 ($PM_{2.5}$ sulfate)	-0.08	-0.27	-0.31	0.83	0.83	0.88	0.34	1					
NO_3 ($PM_{2.5}$ nitrate)	0.40	0.53	0.68	-0.69	-0.47	-0.30	-0.40	-0.54	1				
TC ($PM_{2.5}$ total carbon)	0.77	0.69	0.28	-0.12	0.38	0.36	0.32	-0.04	0.26	1			
EC ($PM_{2.5}$ elemental carbon)	0.90	0.61	0.34	-0.08	0.40	0.46	0.41	0.18	0.20	0.85	1		
OC ($PM_{2.5}$ organic carbon)	0.58	0.64	0.21	-0.13	0.32	0.25	0.22	-0.15	0.26	0.95	0.64	1	
WSMET ($PM_{2.5}$ WS metals)	0.11	-0.19	-0.28	0.61	0.73	0.73	0.42	0.80	-0.47	0.10	0.36	-0.07	1

Time period: gases 1/1/94-6/30/2004 (3834 days), PM_{10} 2/1/1996-6/30/04 (3073 days), $PM_{2.5}$ and components 9/1/1998-6/30/2004 (2130 days)

Table 5.10. Risk ratios, 95% confidence intervals,** and p-values for associations between air pollution levels in the first month of gestation and preterm birth for births in five-county Atlanta stratified by socio-demographic characteristics

	Black		White		Unmarried		<12 years education	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
CO	0.99 (0.95, 1.02)	0.42	1.04 (0.99, 1.09)	0.08	1.00 (0.96, 1.04)	0.85	0.98 (0.93, 1.04)	0.58
NO_2	0.98 (0.96, 1.00)	0.08	1.00 (0.98, 1.03)	0.71	0.98 (0.96, 1.00)	0.06	0.99 (0.96, 1.02)	0.44
SO_2	0.97 (0.95, 0.99)	0.01	0.99 (0.96, 1.02)	0.43	0.97 (0.95, 1.00)	0.04	0.94 (0.91, 0.98)	0.00
O_3	0.95 (0.90, 1.00)	0.06	0.95 (0.88, 1.02)	0.14	0.95 (0.89, 1.00)	0.07	0.97 (0.89, 1.06)	0.49
PM_{10}	0.98 (0.95, 1.01)	0.15	1.00 (0.96, 1.03)	0.89	0.99 (0.96, 1.02)	0.39	1.00 (0.96, 1.04)	0.94
$PM_{2.5}$	1.00 (0.97, 1.03)	0.98	0.99 (0.94, 1.03)	0.50	1.00 (0.96, 1.03)	0.86	1.03 (0.98, 1.08)	0.28
$PM_{2.5-10}$	0.99 (0.96, 1.02)	0.40	0.98 (0.94, 1.02)	0.43	1.00 (0.96, 1.03)	0.86	1.00 (0.95, 1.04)	0.88
$PM_{2.5}$ SO_4	1.00 (0.96, 1.05)	0.98	0.99 (0.93, 1.05)	0.73	0.99 (0.94, 1.04)	0.67	1.01 (0.95, 1.09)	0.69
$PM_{2.5}$ NO_3	1.01 (0.95, 1.07)	0.78	1.01 (0.94, 1.08)	0.85	0.98 (0.92, 1.04)	0.44	1.07 (0.98, 1.16)	0.13
$PM_{2.5}$ OC	1.00 (0.97, 1.03)	0.93	0.97 (0.93, 1.01)	0.10	0.99 (0.96, 1.02)	0.38	1.00 (0.96, 1.04)	0.98
$PM_{2.5}$ EC	1.00 (0.97, 1.03)	0.84	0.98 (0.94, 1.02)	0.37	1.00 (0.97, 1.03)	0.98	1.01 (0.97, 1.06)	0.56
$PM_{2.5}$ TC	1.00 (0.97, 1.03)	0.94	0.97 (0.94, 1.01)	0.14	0.99 (0.96, 1.02)	0.53	1.00 (0.96, 1.05)	0.83
$PM_{2.5}$ WS metals	0.98 (0.93, 1.04)	0.54	1.03 (0.96, 1.10)	0.47	0.99 (0.94, 1.05)	0.81	1.04 (0.96, 1.12)	0.37

** Risk ratios and 95% confidence intervals correspond to an IQR increase in population-weighted spatial average pollutant value for each exposure window reported in Table 5.2

Table 5.11. Risk ratios, 95% confidence intervals,** and p-values for associations between air pollution levels in the week before birth and preterm birth for births in five-county Atlanta stratified by socio-demographic characteristics

	Black		White		Unmarried		<12 years education	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
CO	1.01 (0.98, 1.03)	0.60	0.99 (0.96, 1.02)	0.48	1.02 (1.00, 1.05)	0.07	1.05 (1.01, 1.09)	0.01
NO_2	1.00 (0.98, 1.02)	0.88	0.98 (0.96, 1.01)	0.21	1.01 (0.98, 1.03)	0.60	1.01 (0.98, 1.04)	0.53
SO_2	0.99 (0.97, 1.01)	0.42	0.99 (0.97, 1.02)	0.60	0.99 (0.97, 1.02)	0.63	0.99 (0.96, 1.03)	0.72
O_3	0.99 (0.95, 1.03)	0.58	0.98 (0.94, 1.03)	0.48	1.00 (0.96, 1.04)	0.82	1.02 (0.96, 1.08)	0.49
PM_{10}	0.98 (0.96, 1.01)	0.19	0.98 (0.95, 1.01)	0.23	1.00 (0.98, 1.03)	0.86	1.03 (1.00, 1.07)	0.07
$PM_{2.5}$	0.98 (0.96, 1.01)	0.21	0.98 (0.95, 1.02)	0.29	1.00 (0.97, 1.03)	0.89	1.02 (0.98, 1.06)	0.35
$PM_{2.5-10}$	0.98 (0.96, 1.01)	0.16	1.00 (0.96, 1.03)	0.79	0.98 (0.95, 1.01)	0.16	1.00 (0.96, 1.04)	0.90
$PM_{2.5}$ SO_4	0.98 (0.95, 1.01)	0.22	0.97 (0.93, 1.02)	0.22	1.00 (0.96, 1.03)	0.85	1.03 (0.98, 1.08)	0.24
$PM_{2.5}$ NO_3	0.97 (0.93, 1.01)	0.10	1.01 (0.96, 1.07)	0.64	0.98 (0.95, 1.02)	0.43	1.01 (0.96, 1.07)	0.71
$PM_{2.5}$ OC	0.98 (0.96, 1.00)	0.10	0.98 (0.95, 1.01)	0.25	0.99 (0.96, 1.01)	0.30	1.02 (0.98, 1.05)	0.40
$PM_{2.5}$ EC	1.00 (0.97, 1.02)	0.67	0.98 (0.95, 1.01)	0.26	1.00 (0.98, 1.03)	0.93	1.01 (0.98, 1.05)	0.44
$PM_{2.5}$ TC	0.98 (0.96, 1.01)	0.18	0.98 (0.95, 1.01)	0.23	0.99 (0.97, 1.02)	0.50	1.02 (0.98, 1.05)	0.38
$PM_{2.5}$ WS metals	1.00 (0.96, 1.03)	0.81	0.96 (0.92, 1.01)	0.14	0.99 (0.95, 1.03)	0.51	1.01 (0.96, 1.07)	0.61

** Risk ratios and 95% confidence intervals correspond to an IQR increase in population-weighted spatial average pollutant value for each exposure window reported in Table 5.2

Table 5.12. Risk ratios, 95% confidence intervals,** and p-values for associations between air pollution levels in the final six weeks before birth and preterm birth for births in five-county Atlanta stratified by socio-demographic characteristics

	Black		White		Unmarried		<12 years education	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
CO	0.99 (0.94, 1.04)	0.62	0.95 (0.89, 1.01)	0.10	0.99 (0.94, 1.05)	0.75	1.03 (0.95, 1.11)	0.47
NO_2	1.02 (1.00, 1.05)	0.08	0.97 (0.94, 1.00)	0.08	1.01 (0.98, 1.04)	0.56	1.00 (0.96, 1.04)	0.90
SO_2	0.99 (0.96, 1.02)	0.44	0.98 (0.95, 1.01)	0.20	1.00 (0.97, 1.03)	0.95	1.02 (0.98, 1.06)	0.46
O_3	1.06 (0.98, 1.14)	0.16	0.97 (0.88, 1.07)	0.52	1.01 (0.93, 1.10)	0.81	0.96 (0.85, 1.07)	0.45
PM_{10}	0.98 (0.95, 1.02)	0.39	0.97 (0.93, 1.02)	0.31	0.98 (0.94, 1.02)	0.32	0.99 (0.93, 1.05)	0.74
$PM_{2.5}$	0.98 (0.94, 1.03)	0.49	1.00 (0.94, 1.06)	0.93	0.98 (0.93, 1.03)	0.40	0.96 (0.90, 1.03)	0.30
$PM_{2.5-10}$	1.00 (0.96, 1.04)	0.87	1.03 (0.98, 1.08)	0.31	0.99 (0.94, 1.03)	0.50	0.99 (0.93, 1.05)	0.62
$PM_{2.5}$ SO_4	0.94 (0.87, 1.01)	0.08	0.95 (0.86, 1.05)	0.32	0.95 (0.88, 1.03)	0.19	0.96 (0.86, 1.07)	0.45
$PM_{2.5}$ NO_3	0.97 (0.90, 1.05)	0.45	0.96 (0.87, 1.06)	0.47	0.97 (0.90, 1.05)	0.51	0.96 (0.86, 1.07)	0.46
$PM_{2.5}$ OC	0.99 (0.96, 1.03)	0.78	0.99 (0.95, 1.04)	0.76	0.99 (0.95, 1.03)	0.60	1.00 (0.95, 1.06)	1.00
$PM_{2.5}$ EC	1.00 (0.96, 1.05)	0.94	1.00 (0.94, 1.06)	0.98	0.99 (0.95, 1.04)	0.79	1.02 (0.96, 1.09)	0.46
$PM_{2.5}$ TC	1.00 (0.96, 1.04)	0.85	0.99 (0.94, 1.05)	0.81	0.99 (0.95, 1.03)	0.64	1.01 (0.95, 1.07)	0.85
$PM_{2.5}$ WS metals	0.98 (0.91, 1.07)	0.70	0.96 (0.85, 1.07)	0.43	0.93 (0.85, 1.02)	0.14	0.93 (0.82, 1.05)	0.24

** Risk ratios and 95% confidence intervals correspond to an IQR increase in population-weighted spatial average pollutant value for each exposure window reported in Table 5.2

Table 5.13. Monitor-specific risk ratios and 95% confidence intervals* for preterm birth for births within four miles of the station†

Pollutant Monitor	Dates of Operation	First month of gestation		Final week of gestation		Final 6 weeks of gestation	
		RR (95% CI)	pvalue	RR (95% CI)	pvalue	RR (95% CI)	pvalue
CO DeKalb Tech	9/93- 6/03	0.97 (0.92, 1.01)	0.13	1.03 (1.00, 1.06)	0.07	1.06 (0.99, 1.13)	0.08
CO Roswell Rd.	8/94-12/04	0.98 (0.90, 1.06)	0.58	0.98 (0.93, 1.03)	0.33	0.94 (0.85, 1.05)	0.26
CO Jefferson St.	8/98-12/04	1.02 (0.96, 1.07)	0.53	1.01 (0.98, 1.05)	0.53	0.99 (0.93, 1.06)	0.83
NO_2 Georgia Tech	9/93-12/04	1.02 (0.98, 1.06)	0.30	1.02 (0.98, 1.06)	0.35	1.06 (1.00, 1.12)	0.04
NO_2 Jefferson St.	8/98-12/04	1.02 (0.94, 1.10)	0.70	1.04 (0.97, 1.11)	0.30	1.02 (0.92, 1.13)	0.74
NO_2 Tucker	4/95-12/04	1.01 (0.96, 1.07)	0.62	1.00 (0.94, 1.05)	0.87	1.07 (1.00, 1.15)	0.06
NO_2 South DeKalb	9/93-12/04	1.00 (0.95, 1.04)	0.87	1.01 (0.96, 1.05)	0.80	1.06 (0.99, 1.12)	0.08
O_3 Confederate Ave.	9/93-12/04‡	0.91 (0.78, 1.07)	0.91	0.97 (0.88, 1.07)	0.51	1.00 (0.80, 1.24)	0.99
O_3 South DeKalb	9/93-12/04‡	1.03 (0.75, 1.42)	0.84	1.12 (0.97, 1.28)	0.12	0.87 (0.63, 1.20)	0.39
O_3 Jefferson St.	8/98-12/04	0.94 (0.76, 1.17)	0.60	0.97 (0.84, 1.12)	0.67	1.42 (1.05, 1.91)	0.02
SO_2 Confederate Ave.	9/93-12/04	0.99 (0.95, 1.04)	0.83	0.96 (0.91, 1.00)	0.04	0.96 (0.91, 1.02)	0.24
SO_2 Jefferson St.	8/98-12/04	1.03 (0.96, 1.10)	0.39	1.03 (0.98, 1.09)	0.26	0.98 (0.92, 1.04)	0.53
SO_2 Georgia Tech	9/93-12/04	0.99 (0.93, 1.05)	0.63	1.01 (0.96, 1.06)	0.77	1.01 (0.95, 1.08)	0.71
PM_{10} Jefferson St.	8/98-12/04	1.04 (0.85, 1.28)	0.67	1.11 (0.99, 1.24)	0.07	0.98 (0.73, 1.31)	0.88
PM_{10} Georgia Tech	1/96-12/04	1.08 (0.99, 1.18)	0.10	1.03 (0.96, 1.12)	0.39	1.02 (0.89, 1.17)	0.78
$PM_{2.5}$ Jefferson St.	8/98-12/04	1.09 (0.98, 1.21)	0.11	1.06 (0.98, 1.14)	0.13	1.07 (0.92, 1.24)	0.41
$PM_{2.5}$ Doraville Heath Center	3/99-12/04	0.86 (0.74, 1.01)	0.07	1.02 (0.93, 1.11)	0.69	1.10 (0.85, 1.43)	0.46
$PM_{2.5}$ South DeKalb	3/99-12/04	0.92 (0.79, 1.06)	0.26	0.95 (0.86, 1.04)	0.23	1.24 (0.89, 1.71)	0.20
$PM_{2.5}$ Tucker	3/99-12/04	0.92 (0.77, 1.09)	0.34	1.02 (0.93, 1.12)	0.69	1.00 (0.82, 1.23)	0.99
$PM_{2.5}$ East Rivers School	3/99-12/04	0.94 (0.74, 1.20)	0.64	0.87 (0.77, 0.99)	0.03	1.08 (0.78, 1.49)	0.64
$PM_{2.5}$ Fort McPherson	3/99-12/04	1.05 (0.90, 1.23)	0.53	0.98 (0.89, 1.08)	0.67	0.96 (0.76, 1.22)	0.73
$PM_{2.5-10}$ Jefferson St.	8/98-12/04	1.03 (0.95, 1.12)	0.46	1.03 (0.97, 1.10)	0.30	1.07 (0.97, 1.18)	0.21
$PM_{2.5}$ EC Jefferson St.	8/98-12/04	1.01 (0.93, 1.10)	0.76	1.04 (0.98, 1.10)	0.20	0.97 (0.86, 1.08)	0.55
$PM_{2.5}$ NO_3 Jefferson St.	8/98-12/04	1.03 (0.89, 1.20)	0.68	0.98 (0.90, 1.08)	0.73	0.86 (0.71, 1.04)	0.11
$PM_{2.5}$ OC Jefferson St.	8/98-12/04	1.02 (0.94, 1.10)	0.66	1.01 (0.95, 1.08)	0.75	0.98 (0.89, 1.07)	0.62
$PM_{2.5}$ SO_4 Jefferson St.	8/98-12/04	1.06 (0.94, 1.20)	0.32	1.09 (1.01, 1.19)	0.03	0.93 (0.77, 1.11)	0.42
$PM_{2.5}$ TC Jefferson St.	8/98-12/04	1.02 (0.95, 1.09)	0.67	1.02 (0.96, 1.09)	0.53	0.97 (0.88, 1.08)	0.59
$PM_{2.5}$ WS metals Jefferson St.	8/98-12/04	1.07 (0.93, 1.24)	0.32	1.11 (1.02, 1.22)	0.02	0.89 (0.72, 1.09)	0.26

* Risk ratio and 95% CI's corresponds to a window-specific IQR increase in pollutant levels (shown in Table 5.2).
† Pooled inverse-variance weighted risk ratios for each pollutant and exposure window presented in Table 5.4.
‡ Did not operate in winter months

Section 5.14: Description of population-weighted spatial averaging

In the five-county analyses, daily pollutant concentrations were characterized using a population-weighted spatial average of measurements from all air quality monitors in the study area. We calculated the daily population-weighted spatial averages using the following approach, described in detail by Ivy and colleagues.[1]

1. First, log-transformed pollutant values, on each day, *k*, at each monitoring station, *i*, were standardized using the annual mean and standard deviation at the monitor

$$\beta_{i,k} = \frac{\left(x_{i,k} - E(x_i)\right)}{\sqrt{\text{var}(x_i)}}$$

   where $\beta_{i,k}$ is the standardized pollutant value at monitor *i* on day *k*, $x_{i,k}$ is the log-transformed pollutant concentration at monitor *i* on day *k*, the annual mean of $\beta_i=0$, the annual variance of $\beta_i=1$
2. For each census tract in the study area we created a distance-weighted average of the standardized values from each monitoring station
3. We then converted the standardized value at each census tract back into a pollutant concentration using pollutant-specific distance-decay functions from the most central urban monitor
4. Finally we averaged the pollution values across census tracts, weighting by population counts from the 2000 census

$$C_k = \frac{\sum_j C_{j,k} P_j}{\sum_j P_j}$$

   where C_k is the population-weighted concentration for the five-county Atlanta area on day *k*, P_j is the population in census track *j*, and $C_{j,k}$ is the concentration in census tract *j* on day *k*

1. Ivy D, Mulholland JA, Russell AG. Development of ambient air quality population-weighted metrics for use in time-series health studies. *Journal of the Air and Waste Management Association (in press).*

CHAPTER 6

Ambient air pollution and small for gestational age in Atlanta, 1994-2004: a time-series analysis

[Formatted for *Epidemiology*]

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ABSTRACT

Background: An emerging body of evidence suggests that ambient levels of air pollution during pregnancy may influence fetal growth. **Methods:** To investigate this relationship we used vital record data to construct a retrospective cohort of 453,261 births occurring between 1994 and 2004 in five central counties of metropolitan Atlanta. Using a time-series approach, we examined daily counts of small for gestational age (SGA) in relation to ambient levels of carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone, PM_{10}, $PM_{2.5}$ and speciated PM measurements. Small for gestational age was defined as birth weight at or below the 10th percentile for a given gestational age, sex, race/ethnicity and parity; birth weight percentiles were internally defined using the study population. Separate analyses were conducted for preterm and full term SGA. Daily pollutant levels in five-county Atlanta were characterized using a population-weighted spatial average of air quality monitors in the study area. We also examined ambient concentrations at individual monitors in analyses limited to mothers with residential geocodes within four miles of each station. Relationships between average pollution levels in the first month of gestation, and during a nine week period in the third trimester, were modeled using Poisson generalized linear models. Results were adjusted for seasonal and long-term time trends. **Results:** Results were consistent with little or no association between ambient levels of air pollution and full term SGA. In the analyses limited to mothers residing within four miles of a monitoring station, we observed positive associations between preterm SGA and CO and coarse PM levels in the first month of gestation, and carbonaceous $PM_{2.5}$ in the final nine weeks of pregnancy. **Conclusions:** We observed some evidence for early and late pregnancy effects of air pollution on reduced fetal growth, but only in preterm births. Given the number of comparisons made in this study, these associations should be confirmed in other populations. Because of the morbidity and mortality known to occur in infants who are both small and preterm, the relationship between air pollution and reduced fetal growth in preterm infants could have important public health implications.

INTRODUCTION

Birth weight has long been recognized as a strong predictor of infant morbidity and mortality. Evidence that growth restricted infants are at increased risk of diabetes, hypertension and coronary heart disease later in life magnifies the importance of identifying factors that influence fetal growth.[1] In recent years, numerous epidemiological studies have reported relationships between ambient air pollution and measures of reduced fetal growth.[2-6] To separate effects on fetal growth from effects on length of gestation, investigators have examined low birth weight (<2500 grams) in full term infants,[7-12] birth weight adjusted for gestational age,[7,13-15] and small for gestational age[16-21] (i.e., birth weight below the 10th percentile for gestational age). Many studies suggest an association between fetal growth and ambient particulate matter (PM), although the gestational window of effect has not been consistent across studies. Associations with PM have been reported most commonly for early pregnancy exposures (e.g., first month, first trimester)[7,8,17,19] and late pregnancy exposures (e.g., third trimester),[12,13,22-24] although other investigators have observed associations only in mid-pregnancy or not at all.[9,10,14,16,20] Associations between fetal growth and carbon monoxide (CO) levels in early and late pregnancy have been reported from populations in Southern California, Vancouver, and the Northeastern United States.[10,11,13,19,23,25] Other studies in Denver, Nevada and California failed to show any association.[21,22,26] Evidence from populations outside North America is also mixed, although several investigators report associations with CO levels in early pregnancy.[7-9] Other gaseous pollutants, sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and ozone (O_3), have also been associated with fetal growth in various gestational windows, but not consistently.[7-10,12-14,16,19,20,22,24,25] Several recent reviews of the literature on air pollution and fetal growth conclude that further research is warranted to clarify the gestational windows of susceptibility and identify the specific pollutants associated with fetal growth.[2-6]

Air pollution could act through a number of biological mechanisms to inhibit fetal growth. Pulmonary and placental inflammation, increased blood coagulation and viscosity, and

altered endothelial and vascular function could compromise uteroplacental blood flow and inhibit the placental transfer of oxygen and nutrients from mother to fetus.[27] Some of these mechanisms are thought to be involved in the well-documented relationship between maternal active and passive smoking and fetal growth restriction.[28-30] Evidence from studies of maternal smoking suggests that the third trimester is a particularly vulnerable exposure window.[30-32] Furthermore, the third trimester corresponds to the period of most rapid fetal growth and fat accumulation.[28] Early pregnancy may also be a period of vulnerability, with abnormal reaction between trophoblast and uterine tissue around the time of implantation leading to chronic placental insufficiency throughout pregnancy.[33] Furthermore, recently toxicological evidence in mice suggests that early pregnancy exposures to air pollution may be the most damaging.[34]

To investigate the relationship between ambient levels of air pollution during pregnancy and small for gestational age (SGA), we conducted a time-series analysis in the central five-county area of metropolitan Atlanta over the period 1994-2004. We examined all US Environmental Protection Agency (EPA) criteria pollutants (O_3, SO_2, NO_2, CO, PM_{10}, $PM_{2.5}$), as well as speciated particle measurements which are rarely available and have not been previously assessed in relation to measures of fetal growth. We focused on two gestational windows of interest based on previous air pollution studies, studies of maternal active and passive smoking and toxicological evidence: the first month of gestation and the third trimester. Our objective was to assess whether ambient pollution levels during selected gestational windows are associated with rates of SGA.

METHODS

Study Population

We obtained Georgia vital record data for births to mothers residing in the five central counties of the Atlanta metropolitan area from the Office of Health Research and Policy, Georgia Division of Public Health. The study area, shown in Figure 6.1, included 1752 square miles (4538

km^2), an area with a radius 16 miles (25.7 km) at its narrowest and 32 miles (51.5 km) at its widest. The cohort included singleton infants who reached at least 20 weeks of gestation and were born between January 1, 1994 and December 31, 2004 without major structural congenital birth defects. We further restricted inclusion to African American, white, or Hispanic infants because there were too few births in other race/ethnicity groups to construct reliable birth weight percentiles. In addition, 12,370 (2.4%) infants were excluded due to missing data on maternal marital status, education, parity or gestational age. After exclusions, 453,261 out of 509,776 births (88.9%) in the five-county area between January 1, 1994 and December 31, 2004 were eligible for analysis. There were 379,723 eligible births after January 1, 1996, when daily PM_{10} monitoring data began, and there were 280,956 eligible births after August 1, 1998, when $PM_{2.5}$ and speciated PM monitoring began.

Outcome definition

An infant whose birth weight was equal to or below the 10th percentile for his or her gestational age, sex, parity (primiparous, multiparous) and race/ethnicity (black, white and Hispanic) was classified as SGA. The 10th percentile birth weight values were determined internally using the study population so that we could maximize our sample size; a sex-, race-, and parity-specific national reference for Hispanic ethnicity was not available. Tenth percentiles of birth weight for gestational age for our study population are shown in Table C1 in Appendix C. Although the dichotomous outcome of SGA imperfectly discriminates between physiological and pathological smallness, SGA is commonly used as a proxy for intrauterine growth restriction because it identifies a subset of neonates at higher risk of perinatal mortality and morbidity.[35] Whether diagnosis of SGA should be made within strata of race and parity is a matter of debate in the literature.[36-40] In this analysis, where rates of SGA are contrasted within the same geographic population across time, we chose to incorporate race and parity into the definition of SGA to

account for some of the variation in birth weight for gestational age due to factors other than air pollution.

Intrauterine growth restriction and preterm birth are not independent pathologies. Induced preterm births can be medically indicated by intrauterine growth restriction, and studies utilizing *in utero* growth curves of term births instead of live birth weights to construct weight for gestational age percentiles find that 20% or more of spontaneous preterm births are classified as SGA.[37,41,42] Because preterm births are more likely to have experienced intrauterine growth restriction than term births, a 10th percentile birth weight threshold based on live birth weights identifies a more severely growth restricted group in preterm births compared to full term births. Therefore, we conducted separate analyses for preterm and term infants. This approach also allowed for comparison of results with most previous studies which were limited to full term infants.[7,9-12,14,17-19,21,23,25,43]

For 98.6% of the cohort, gestational age was calculated using the reported date of the last menstrual period (LMP). The clinical estimate of gestational age was substituted for the remaining 1.4% of births whose LMP date was missing or yielded an implausible gestational age of <20 or >44 weeks. Counts of SGA were determined for each day, either by conception date, birth date or on the first day of the 37th week of gestation, depending on the gestational window of exposure being investigated. In the analysis, the daily counts of SGA (numerator) were offset by the number of infants at risk each day (denominator) which also differed by exposure window and is discussed in greater detail below.

Ambient Air Quality Data

We obtained ambient air pollution levels from three sources: 1) the U.S. EPA Air Quality System, 2) the Georgia Institute of Technology $PM_{2.5}$ network, and 3) the Aerosol Research and Inhalation Epidemiology Study (ARIES) monitor located in downtown Atlanta. The daily air metrics obtained included 1-hour maximum carbon monoxide (CO), 1-hour maximum

nitrogen dioxide (NO_2), 1-hour maximum sulfur dioxide (SO_2), 8-hour maximum ozone (O_3), and 24-hour average PM_{10}, $PM_{2.5}$, and $PM_{2.5}$ components. Gaseous pollutants were available for the entire study period. Daily PM_{10} monitoring began in January 1996 and $PM_{2.5}$ and PM component monitoring began in August 1998.

For CO, NO_2, SO_2, O_3, PM_{10} and $PM_{2.5}$, we calculated a population-weighted spatial average for each day in the study area using a method described in detail by Ivy and colleagues.[44] This approach took advantage of all the monitoring data available for each pollutant on a given day and yielded a daily spatial composite metric robust to missing data at individual monitoring sites. In addition, population-weighting the ambient measures may have improved longitudinal correlations with average population exposures. There were five CO monitors, six NO_2 monitors, five SO_2 monitors, five O_3 monitors, nine PM_{10} monitors and eleven $PM_{2.5}$ monitors used to calculate the daily spatial averages. For the particle component measurements, $PM_{2.5-10}$, $PM_{2.5}$ sulfate, $PM_{2.5}$ nitrate, $PM_{2.5}$ organic carbon, $PM_{2.5}$ elemental carbon, $PM_{2.5}$ total carbon, and $PM_{2.5}$ water-soluble metals, daily measurements from the centrally located ARIES monitor were used. Ozone measurements were missing for six winter months between 1994 and 1996, when ozone levels are consistently low. We imputed these missing ozone values using results of a model in which temperature and week of year predicted the nonmissing ozone values. Predicted ozone values from the model were highly correlated with measured ozone values in winters after 1996 when ozone was monitored (r=0.92 for four-week averages).

Exposure Assignment

Daily population-weighted pollutant values were averaged over the gestational window of interest for analysis in the time series. For all pollutants and gestational windows of interest, an exposure was assigned only when at least 85% of days in the averaging window had available pollution data; otherwise the exposure assignment was set to missing, with the exception of imputed winter ozone values described above.

In a complementary approach, instead of using the five-county population-weighted spatial average for each pollutant, we created spatial capture areas around each monitor and conducted monitor-specific time-series analyses for the cohort of infants with residential geocodes within four miles of the station. This approach allowed for the possibility that ambient measurements close to the maternal residential address might better correlate with personal exposures, particularly for primary pollutants which are more spatially heterogeneous (e.g., SO_2 CO, NO_2). For some pollutants, the four-mile buffers around monitoring stations overlapped; in such cases, maternal addresses within four miles of more than one station were assigned to the closest monitor. The capture areas were identical throughout the study period, but as a result of the overlap, were not necessarily perfect circles. We limited these monitor-specific analyses to monitors that recorded daily pollutant concentrations. Thus, $PM_{2.5}$ and PM_{10} monitors which recorded levels every three or six days were not included in this approach. As in the five-county analysis, an exposure was assigned only when at least 85% of the daily measurements in the exposure window were available.

Analytic approach

Daily counts of SGA were analyzed using Poisson generalized linear models. Pollutants were examined as continuous variables in single-pollutant models, using scaled variance estimates to account for possible Poisson overdispersion. In the spatial capture area approach, separate time-series analyses were run for the area surrounding each monitor, and effect estimates were pooled using inverse-variance weights to obtain a summary risk ratio for each pollutant. All analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Because ambient air pollution levels exhibit strong seasonal variation, and birth weight may also vary by season,[45] we smoothly controlled for seasonal trends using parametric cubic splines. We constrained the seasonal parameters in the model to be the same across all study years by including a day of year spline (day=1 to 365) with 12 monthly knots. In our descriptive

analyses we observed racial, educational and marital status differences in the seasonality of birth; seasonal patterns of birth were similar across maternal age groups and parity. For example, births in the spring were more likely to be to mothers who were white, college-educated and married. Because these socio-demographic factors are related to fetal growth, we accounted for these seasonal trends explicitly by modeling temporal associations within educational (<12 years, 12-15 years, 16+ years) and marital status (married, unmarried) groups. Thus, each study day had multiple observations representing the counts of SGA within educational and marital status strata. Race was inherently controlled for in the outcome, as SGA was determined within strata of race/ethnicity. Accounting for these subtle trends directly allowed the day of year spline to adjust for other seasonal influences on the risk of SGA. We smoothly adjusted for long-term temporal trends in SGA using a second cubic spline with knots on June 30th of each year.

First-month-of-gestation exposure window

To examine pollution levels during the first month of gestation, births were aggregated by conception date, assumed to be 14 days after the LMP date, and each conception date was assigned the average pollution level over the subsequent four weeks. Models took the form:

$$\log[E(Y_{t,k,m})] = \text{offset}_{t,k,m} + \alpha + \beta(\text{pollutant}_t) + \Sigma_{i=1\text{-}14}(\delta_i)(\text{long-term cubic spline}_t)$$
$$+ \Sigma_{j=1\text{-}15}(\gamma_j)(\text{seasonal cubic spline}_t) + \Sigma_{q=1\text{-}2}(\phi_q)(\text{education}_k) + \pi(\text{marital status}_m)$$

where$Y_{t,k,m}$ represents the number of conceptions on day *t* within strata of education (*k*) and marital status (*m*) who were eventually born SGA. The SGA outcome inherently controls for race/ethnicity, sex and parity. The count was offset by the total number of conceptions on day *t* within the same educational and marital stratum; only conceptions who eventually reached 20 weeks gestation could be identified. The count of SGA infants conceived on a given date was the outcome variable used to evaluate the hypothesis that high levels of air pollution could lead to

suboptimal fetal growth through disruption of the implantation and placentation process early in pregnancy.

Third trimester exposure windows

The third trimester exposure window was defined differently for full term and preterm infants because not all preterm births reach the third trimester. In the full term birth analyses we aggregated births by the first day of their 37th week (day 259); by definition, every term birth reached at least 37 weeks gestation. Pollution assigned to each day reflected the average exposure in the previous nine weeks corresponding to weeks 28 through 36 of gestation. Although this time period did not capture the entirety of the third trimester for infants born after 37 weeks, the exposure period included the period of highest fetal growth velocity[46] and allowed us to contrast exposures during the same gestational window in every infant. The models took the following form:

$$\log[E(Y_{t,k,m})] = \text{offset}_{t,k,m} + \alpha + \beta(\text{pollutant}_t) + \Sigma_{i=1\text{-}14}(\delta_i)(\text{long-term cubic spline}_t) + \Sigma_{j=1\text{-}15}(\gamma_j)(\text{seasonal cubic spline}_t) + \Sigma_{q=1\text{-}2}(\phi_q)(\text{education}_k) + \psi(\text{marital status})$$

where $Y_{t,k,m}$ represents the number of full term SGA infants who reach their 37th week of gestation on day *t*, within strata of education (<12 years, 12-15 years, 16+ years), and marital status (married, unmarried). The offset, or denominator, is the total number of full term infants who reach the 37th week of gestation on day *t*, within strata of education (*k*) and marital status (*m*). The pollutant concentration represents the average concentration in the Atlanta area over the previous nine weeks. Because it is possible that an infant could be growth restricted in gestational weeks 28-36 and then experience catch-up growth before birth, we conducted sensitivity analyses examining pollution levels in the nine weeks leading up to birth. In this

sensitivity analysis, counts of full term SGA were aggregated by birth date instead of the first day of gestational week 37.

In the preterm SGA analyses, counts of preterm SGA were aggregated by birth date and analyzed in relation to air pollution levels in the nine weeks preceding birth. The number of preterm SGA births each day was offset by the total number of preterm births on the study day. For most preterm infants, this nine-week window fell primarily in the third trimester; however, in very preterm infants who are born before the third trimester, the exposure window fell in the second trimester.

RESULTS

In the full five-county cohort, 10.5% of births (47,775) were classified as SGA; on average there were 10.7 full term SGA births per day and 1.2 preterm SGA births per day over the study period. Maternal and infant characteristics of the five-county cohort and the cohort of births within four miles of a monitor, stratified by preterm status, are displayed in Table 6.1. Compared to the full five-county cohort, mothers residing within four miles of a monitor were younger, less educated and more likely to be African American and unmarried.

Descriptive statistics of the five-county pollutant averages for each exposure window are presented in Table 6.2. Included in the table is the number of observation days used in each analysis, which differed by air quality data completeness and the days for which the risk set could be identified. For example, conceptions at risk could not be identified for much of 2004 because these conceptions correspond to birth records from 2005, and records from 2005 were not collected for this study. Correlations between the pollutants for the two averaging windows are available in Tables C2 and C3 in Appendix C. Very few days were excluded in the five-county analysis based on the minimum 85% completeness criteria for CO (0%), NO_2 (0.7%), SO_2 (1.7%), O_3 (0%), PM_{10} (1.7%) and $PM_{2.5}$ (0%). For the speciated PM components limited to the ARIES monitoring station, a larger percentage of exposure assignments were excluded based on the 85%

completeness criteria: $PM_{2.5-10}$ (13.3%), $PM_{2.5}$ sulfate (19.6%), $PM_{2.5}$ nitrate (19.7%), $PM_{2.5}$ total carbon (2.1%), $PM_{2.5}$ elemental carbon (2.1%), and $PM_{2.5}$ organic carbon (2.1%), and $PM_{2.5}$ water-soluble metals (19.1%). The percentage missing data reported above corresponds to the four-week exposure window; the nine-week exposure window had similar degrees of missing exposure assignments.

Five-county analysis

Risk ratios and 95% confidence intervals for the five-county analysis are presented in Table 6.3. Risk ratios correspond to the relative increase in risk for one IQR increase in window-specific pollutant levels (IQRs shown in Table 6.2). Results were consistent with little or no association for both preterm and full term infants in both gestational windows examined. In full term infants the risk ratios for $PM_{2.5}$ and CO, two pollutants of *a priori* interest, were 1.00 (95% CI: 0.98-1.03) and 1.00 (95% CI: 0.97-1.03), respectively, for levels in the first month of gestation; risk ratios were similarly null for levels in gestational weeks 28-36. We observed one inverse association between $PM_{2.5}$ in the nine weeks before birth and preterm SGA; however, the upper confidence limit was close to 1.00. In sensitivity analyses of the full term cohort, assignment of pollution levels in the nine-weeks before birth instead of gestational weeks 28-36 did not meaningfully change the results (see Table C6 in Appendix C).

Capture area analysis

Risk ratios and 95% confidence intervals for the population of pregnancies within four miles of a monitor are presented in Table 6.4. These pooled, inverse-variance weighted risk ratios are scaled to the same IQR values used in the five-county analysis; monitor-specific results are shown in tables C4 and C5 in Appendix C. The number of monitor-specific estimates incorporated into the pooled estimate and the number of births captured by the four-mile buffers for each pollutant are also shown in Table 6.4. For both gestational windows, results were

consistent with little or no association between the pollutants examined and full term SGA. Risk ratios were close to 1.00 for most pollutants, although confidence intervals were wider relative to the five-county analysis reflecting the smaller number of births included. Sensitivity analyses of pollution levels in the nine weeks preceding birth were also consistent with little or no association.

In the preterm birth capture area analyses, we observed several positive associations. Preterm SGA was associated with CO levels in the first month of gestation (RR=1.12, 95% CI =1.02-1.23) as well as $PM_{2.5-10}$ levels in the first month of gestation (RR=1.34, 95% CI=1.01-1.78). We observed associations between preterm SGA and $PM_{2.5}$ total carbon (RR=1.58, 95% CI=1.04-2.39) and $PM_{2.5}$ elemental carbon (RR=1.61, 95% CI=1.05-2.47) in the nine weeks before birth; $PM_{2.5}$ organic carbon was also suggestive (RR=1.41, 95% CI= 1.00-1.98). As shown in Table C3 in Appendix C, the carbon fractions of $PM_{2.5}$ are highly correlated. The observed associations with $PM_{2.5-10}$ and the carbon fractions of $PM_{2.5}$ reflect associations solely around the ARIES monitor because no other monitors in our study area measured these pollutants; associations observed for these pollutants had fairly wide 95% confidence intervals. Carbon monoxide was measured at three monitoring stations, and risk ratio estimates for CO levels in the first month of pregnancy were elevated at all three sites, although lower 95% confidence intervals included 1.00 at two of the monitors. For a 0.3 ppm increase in CO in the first month of pregnancy, estimated risk ratios were 1.15 (95% CI=1.01-1.30) at the DeKalb Tech monitor, 1.09 (95% CI=0.85-1.40) at the Roswell Road monitor and 1.08 (95% CI=0.91-1.28) at the Jefferson St. ARIES monitor.

DISCUSSION

In this time-series study, we examined the relationship between 13 air pollutants during two gestational windows and small for gestational age in full term and preterm infants. We did not observe any evidence of an association between full term SGA and ambient air pollution

levels in the selected gestational windows of interest. When analyses were restricted to mothers residing within four miles of a monitor, preterm SGA was associated with CO and $PM_{2.5-10}$ levels in the first month of pregnancy as well as the carbon fractions of $PM_{2.5}$ in the final nine weeks of pregnancy.

To our knowledge, previous investigators have not examined measures of reduced fetal growth in relation to air pollution levels specifically in preterm infants. However, numerous studies have reported associations between air pollution and preterm birth.[3,14,23,47,48] If intrauterine growth restriction is a cause of preterm birth, and air pollution is a cause of intrauterine growth restriction, air pollution would also cause preterm birth through the pathway of restricted fetal growth.

In this study, the associations observed between preterm SGA and CO and carbonaceous $PM_{2.5,}$ two primary pollutants emitted from traffic, suggest a role for traffic-related pollution in fetal growth. Previous studies have also commonly implicated traffic-related pollutants. However, these studies were all limited to full term infants.[7,8,11,19,21,23,25,43] In this study we did not observe positive associations between traffic-related air pollutants, or any other air pollutants, and full term SGA. Coarse particles between 2.5 and 10 microns in aerodiameter, which were also associated with preterm SGA in the first month of gestation, are from a mix of sources including soil and street dust, tire wear debris, plant and animal fragments, and coal and oil fly ash. These particles are mechanically generated as opposed to the chemical reactions that form fine particles.[49] Although not respirable, these particles are small enough to reach the thoracic region of the respiratory tract.

Inconsistent results among the studies conducted to date may reflect differences in pollution levels and composition across locations, outcome definitions, exposure assessment or population characteristics and behaviors. In addition, because evidence is not consistent with regard to the gestational window(s) of vulnerability and the specific pollutants of harm, most investigators have examined multiple pollutants over multiple gestational windows; as a result,

some of the seemingly contradictory results may be attributable to Type I errors. Inconsistent results may also be due to differences in analytic approach or inadequate control for confounders. In both the five-county and capture area analyses in this study, comparisons were made across days instead of individuals in order to reduce the plausibility of confounding by individual level risk factors, which are unlikely to be associated with short-term fluctuations in air pollution. Residual confounding by factors such as socioeconomic status (SES), which are difficult to quantify, may be a concern in studies which utilize spatial contrasts of exposure.[50]

In our examination of preterm SGA, our two approaches to exposure assignment provided different results. Associations were observed in the capture area analysis but not the five-county analysis, although the effect estimate for first month CO levels was also suggestive in the five-county approach (RR=1.06; 95% CI=0.98-1.15). Assuming these associations are not due to chance, it is possible that the finer spatial scale of exposure assignment used in the capture area analysis better approximated exposures for mothers living near the monitor, particularly for spatially heterogeneous pollutants such as CO, $PM_{2.5-10}$ and the carbon fractions of $PM_{2.5}$.[44,51] Although this approach is intuitively appealing, it is unclear whether measurements from the closest monitor better correlate with personal exposures when compared to a city-wide metric.[52,53] Pregnant women may spend a large portion of their day away from their residence, and with about 20% of women in Atlanta changing residences during pregnancy, exposure assignment based on the residence at time of birth is problematic for assessment of early gestational windows.[54,55]

Differing results from the two approaches may also reflect differences in population susceptibility. Notably, mothers residing near a monitor were more likely to be black, young, unmarried and less educated. Increased sensitivity to the adverse effects of air pollution in lower SES groups, for example, could be explained by a lack of access to health care, nutritional deficiencies,[27] or concurrent exposure to other occupational and environmental hazards. Effect modification by SES-related characteristics could also act indirectly through better exposure

assessment in these individuals; lower SES groups may be more exposed to ambient air because of less access to air conditioning, greater infiltration of ambient pollutants into older, inner city housing,[56] and occupations or daily activity patterns which involve more time spent outdoors. In fact, several previous studies have reported stronger associations between air pollution and adverse birth outcomes in minority and lower SES women. In California, Wilhelm and Ritz found stronger associations between traffic sources and term LBW in lower SES census tracts[43]; Bell and colleagues recently reported stronger associations between $PM_{2.5}$ and restricted fetal growth for black women compared to white.[13]

Measurement error in both the air pollution exposure and vital records is a limitation of our study as well as previous studies. In the temporal analytic setting, the likely result of using ambient levels of air pollution as a proxy for personal exposures would be to attenuate associations.[57] This might explain some of the null results we observed, but would be unlikely to induce spurious associations. Although birth weight is thought to be accurately recorded on birth records, gestational age is undoubtedly misclassified on many birth records in our study.[58,59] Measurement error in gestational age would lead to misclassification in the outcome of small for gestational age. Furthermore, the classification of small for gestational age is an imperfect proxy for intrauterine growth restriction. Some constitutionally small infants are considered small for gestational age, and some infants who experienced intrauterine growth restriction weigh above the 10th percentile for their gestational age at birth. Outcome misclassification may have created a bias toward the null but would be unlikely to induce a spurious association because the degree and direction of the misclassification is unlikely to be associated with short-term temporal changes in air pollution.

A limitation of examining early gestational windows is the inability to identify all conceptions; in our study we could only identify fetuses who survived to 20 weeks and delivered within the state of Georgia. If early pregnancy exposure to air pollution increases the risk of fetal loss in addition to restricting fetal growth, associations between air pollution and SGA would be

underestimated. We identified likely gestational windows of vulnerability based on the findings from previous air pollution and fetal growth studies, studies of maternal active and passive smoking and toxicological evidence. However, it is possible that we misspecified the critical gestational windows for air pollution exposures.

In summary, we observed evidence of an effect for early pregnancy CO and $PM_{2.5-10}$, and late pregnancy carbonaceous $PM_{2.5}$ on the risk of SGA, but only in preterm births. These findings should be interpreted with caution in light of the many relationships investigated and lack of *a priori* evidence for an effect of these pollutants in preterm births. Nonetheless, increased risk of SGA in preterm infants could have important public health implications, as infants who are both small and preterm experience high rates of morbidity and mortality.[35,60] Future studies should include preterm infants when investigating the fetal growth effects of air pollution. Unlike previous studies, we did not find evidence of a relationship between air pollution and reduced fetal growth in full term infants.

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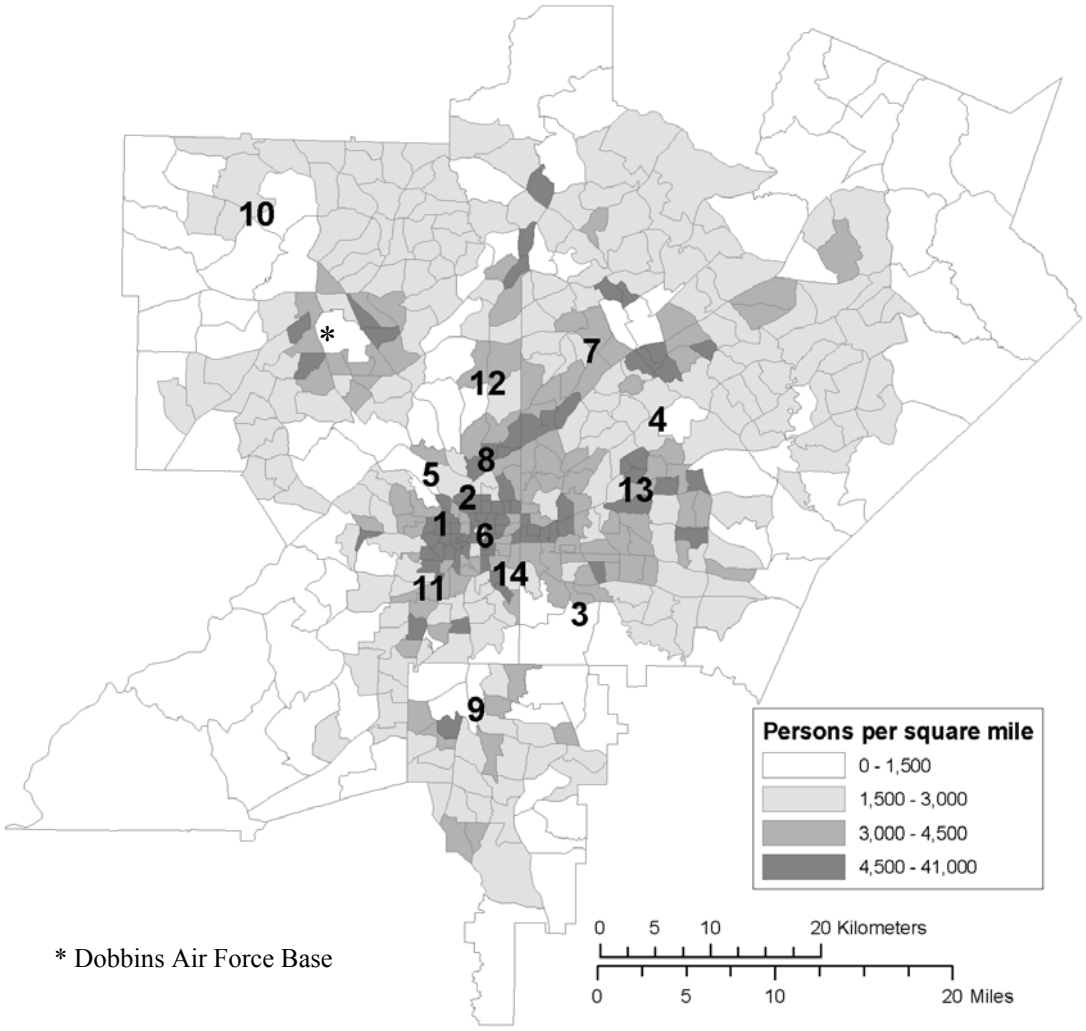


Figure 6.1. Five-county Atlanta study area, population density and location of ambient air quality monitoring stations

1. Jefferson St: CO, NO_2, SO_2, O_3, PM_{10}, $PM_{2.5}$, PM components
2. Georgia Tech: NO_2, SO_2, PM_{10}
3. South DeKalb: NO_2, O_3, $PM_{2.5}$
4. Tucker: NO_2, $PM_{2.5}$
5. Fire Station 8: $PM_{10,}$ $PM_{2.5}$
6. Fulton Health Dept: PM_{10}
7. Doraville Health Center: $PM_{10,}$ $PM_{2.5}$
8. East Rivers School: $PM_{10,}$ $PM_{2.5}$
9. Forest Park: $PM_{2.5}$
10. Kennesaw: $PM_{2.5}$
11. Fort McPherson: $PM_{2.5}$
12. Roswell Road: CO
13. DeKalb Tech: CO
14. Confederate Ave: SO_2, O_3

Table 6.1. Maternal and infant characteristics for births in five-county Atlanta, January 1, 1994-December 31, 2004, and for births within four miles of a monitoring station

	Five-county Atlanta Full Term Births (N=406,627)* Number (%)	Five-county Atlanta Preterm Births (N=46,634)* Number (%)	Near a monitor (4 mi) Full Term Births (N=110,357)* Number (%)	Near a monitor (4 mi) Preterm Births (N=14,544)* Number (%)
SGA	42,818 (10.5%)	4,937 (10.6%)	12,244 (11.1%)	1,506 (10.4%)
Female	200,748 (49.4%)	21,906 (47.0%)	54,590 (49.5%)	6,857 (47.2%)
Maternal age group (years)				
<20	42,420 (10.4%)	6,198 (13.3%)	15,282 (13.9%)	2,431 (16.7%)
20-34	303,755 (74.7%)	32,965 (70.7%)	80,113 (72.6%)	10,093 (69.4%)
35+	60,452 (14.9%)	7,471 (16.0%)	14,962 (13.6%)	2,020 (13.9%)
Maternal race				
White	183,946 (45.2%)	15,684 (33.6%)	29,962 (27.2%)	2,441 (16.8%)
African American	164,731 (40.5%)	25,617 (54.9%)	63,712 (57.7%)	10,450 (71.9%)
Hispanic	57,950 (14.3%)	5,333 (11.4%)	16,683 (15.1%)	1,653 (11.4%)
Maternal Education (completed years)				
<12	78,926 (19.4%)	10,482 (22.5%)	28,761 (26.1%)	4,312 (29.7%)
12-15	189,818 (46.7%)	24,031 (51.5%)	50,709 (45.9%)	7,493 (51.5%)
16+	137,883 (33.9%)	12,121 (26.0%)	30,887 (28.0%)	2,739 (18.8%)
Married	262,769 (64.6%)	24,773 (53.1%)	55,574 (50.4%)	5,548 (38.2%)
First birth	176,592 (43.4%)	20,049 (43.0%)	48,763 (44.2%)	5,908 (40.6%)
Reported tobacco use	19,236 (4.7%)	3,516 (7.5%)	4,603 (4.2%)	1,132 (7.8%)
Season of birth				
Winter (December-February)	99,477 (24.5%)	11,522 (24.7%)	27,120 (24.6%)	3,573 (24.6%)
Spring (March-May)	100,640 (24.8%)	11,387 (24.4%)	26,660 (24.2%)	3,564 (24.5%)
Summer (June-August)	103,945 (25.6%)	12,045 (25.8%)	27,945 (25.3%)	3,664 (25.2%)
Fall (September-November)	102,565 (25.2%)	11,680 (25.1%)	28,632 (25.9%)	3,743 (25.7%)
Year of birth				
1994	32,577 (8.0%)	3,847 (8.3%)	6,241 (5.7%)	967 (6.7%)
1995	33,272 (8.2%)	3,842 (8.2%)	7,616 (6.9%)	1,136 (7.8%)
1996	33,611 (8.3%)	3,751 (8.0%)	8,012 (7.3%)	1,010 (6.9%)
1997	34,888 (8.6%)	3,796 (8.1%)	8,130 (7.4%)	1,047 (7.2%)
1998	35,730 (8.8%)	3,940 (8.5%)	8,867 (8.0%)	1,077 (7.4%)
1999	37,044 (9.1%)	4,097 (8.8%)	10,068 (9.1%)	1,210 (8.3%)
2000	39,661 (9.8%)	4,393 (9.4%)	11,445 (10.4%)	1,391 (9.6%)
2001	40,362 (9.9%)	4,741 (10.2%)	13,028 (11.8%)	1,734 (11.9%)
2002	39,901 (9.8%)	4,586 (9.8%)	12,659 (11.5%)	1,577 (10.8%)
2003	39,648 (9.8%)	4,925 (10.6%)	12,269 (11.1%)	1,690 (11.6%)
2004	39,933 (9.8%)	4,716 (10.1%)	12,022 (10.9%)	1,705 (11.7%)

*Limited to black, white and Hispanic race/ethnicity, excludes plural births, major structural congenital birth defects, and missing parity, education, marital status and gestational age information

Table 6.2. Descriptive statistics of pollution levels for each pollution averaging window using the population-weighted spatial composite pollutant values (gaseous pollutants, PM_{10} and $PM_{2.5}$) and the ARIES station measurements ($PM_{2.5-10}$ and $PM_{2.5}$ components).

POLLUTANT	9-week average §				4-week average ‡			
	N*	Mean ± SD	IQR**	Range	N*	Mean ± SD	IQR**	Range
1-hour max carbon monoxide (ppm)	3957	0.90 ± 0.20	0.3	0.48-1.40	3833	0.93 ± 0.22	0.3	0.52-1.70
1-hour max nitrogen dioxide (ppb)	3957	23.4 ± 3.2	5	15.4-31.4	3807	23.5 ± 4.0	5	12.6-38.5
1-hour max sulfur dioxide (ppb)	3919	10.3 ± 2.4	3	5.1-21.2	3769	10.5 ± 3.1	4	3.9-22.7
8-hour max ozone (ppb)	3957	44.4 ± 13.6	24	20.6-82.4	3833	44.1 ± 15.0	25	18.7-90.1
24-hour PM_{10} ($\mu g/m^3$)	3167	24.0 ± 5.1	7	14.0-39.7	2929	23.9 ±6.3	8	10.8-51.8
24-hour $PM_{2.5}$ ($\mu g/m^3$)	2223	16.4 ± 3.3	4	10.6-28.8	2038	16.6 ±4.1	5	9.8-34.1
24-hour $PM_{2.5-10}$ ($\mu g/m^3$)	1930	9.0 ± 1.9	2.3	5.3-15.8	1765	9.1 ± 2.5	2.7	4.6-19.2
24-hour $PM_{2.5}$ sulfate ($\mu g/m^3$)	1776	5.0 ± 1.9	2.9	2.0-11.6	1638	5.0 ± 2.3	2.8	1.9-13.3
24-hour $PM_{2.5}$ nitrate ($\mu g/m^3$)	1733	0.89 ± 0.42	0.6	0.32-2.53	1635	0.99±0.49	0.7	0.30-2.67
24-hour $PM_{2.5}$ total carbon ($\mu g/m^3$)	2222	6.0 ± 1.0	1.6	4.1-8.7	1995	6.0 ±1.4	1.7	3.3-11.4
24-hour $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	2222	1.62 ± 0.44	0.5	1.05-3.26	1995	1.65±0.55	0.5	0.78-4.31
24-hour $PM_{2.5}$ organic carbon ($\mu g/m^3$)	2222	4.3 ± 0.7	1.0	2.9-6.3	1995	4.4 ±1.0	1.3	2.4-8.3
24-hour $PM_{2.5}$ water-soluble metals † ($\mu g/m^3$)	1776	0.031 ± 0.011	0.017	0.011-0.071	1648	0.031 ±0.013	0.017	0.009-0.090

§ Time period: gases 1/1/1994-10/31/2004 (3957 days), PM_{10} 3/1/1996-10/31/2004 (3167 days), $PM_{2.5}$ 10/1/1998-10/31/2004 (2223 days)

‡ Time period: gases 9/1/93-2/28/2004 (3833 days), PM_{10} 1/1/1996-2/28/2004 (2981 days), $PM_{2.5}$ 8/1/1998-2/28/2004 (2038 days)

* Number of days over time period with nonmissing pollution values

** Interquartile range (75^{th} percentile- 25^{th} percentile)

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table 6.3. Risk ratios and 95% confidence intervals for ambient air pollution levels in selected gestational windows and SGA for births in five-county Atlanta

	Full Term Births		Preterm Birth	
	First month of gestation ¥ RR (95% CI)	Weeks 28-36 of gestation Ψ RR (95% CI)	First month of gestation ¥ RR (95% CI)	Final 9 weeks of gestation ‡ RR (95% CI)
1-h max CO (ppm)	1.00 (0.97, 1.03)	1.00 (0.96, 1.05)	1.06 (0.98, 1.15)	0.94 (0.83, 1.07)
1-h max NO_2 (ppb)	0.99 (0.98, 1.01)	1.01 (0.98, 1.03)	0.99 (0.95, 1.03)	0.97 (0.91, 1.03)
1-h max SO_2 (ppb)	0.98 (0.96, 1.00)	1.00 (0.98, 1.03)	1.02 (0.97, 1.08)	1.02 (0.96, 1.08)
8-h max O_3 (ppb)	1.00 (0.96, 1.05)	0.98 (0.92, 1.04)	0.95 (0.84, 1.08)	0.87 (0.73, 1.05)
24-h PM_{10} ($\mu g/m^3$)	1.00 (0.98, 1.02)	0.98 (0.95, 1.01)	0.99 (0.94, 1.06)	0.94 (0.86, 1.03)
24-h $PM_{2.5}$ ($\mu g/m^3$)	1.00 (0.98, 1.03)	1.00 (0.96, 1.03)	0.98 (0.91, 1.06)	0.90 (0.82, 0.99)*
24-h $PM_{2.5-10}$ ($\mu g/m^3$)	1.02 (1.00, 1.05)	1.00 (0.97, 1.03)	1.02 (0.95, 1.09)	0.97 (0.89, 1.05)
24-h $PM_{2.5}$ sulfate ($\mu g/m^3$)	0.98 (0.95, 1.02)	0.96 (0.90, 1.02)	0.97 (0.87, 1.07)	0.99 (0.83, 1.19)
24-h $PM_{2.5}$ nitrate ($\mu g/m^3$)	0.96 (0.92, 1.00)	0.97 (0.92, 1.03)	0.98 (0.86, 1.12)	0.95 (0.80, 1.12)
24-h $PM_{2.5}$ total carbon ($\mu g/m^3$)	1.01 (0.99, 1.04)	0.99 (0.96, 1.03)	1.01 (0.95, 1.08)	0.93 (0.83, 1.03)
24-h $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	1.00 (0.98, 1.02)	1.00 (0.97, 1.04)	1.01 (0.95, 1.08)	0.93 (0.84, 1.04)
24-h $PM_{2.5}$ organic carbon ($\mu g/m^3$)	1.02 (0.99, 1.04)	0.99 (0.96, 1.02)	1.01 (0.95, 1.08)	0.94 (0.86, 1.03)
24-h $PM_{2.5}$ water-soluble metals† ($\mu g/m^3$)	0.98 (0.94, 1.03)	0.98 (0.91, 1.06)	1.07 (0.95, 1.21)	0.82 (0.66, 1.03)

* $p<0.05$

** Risk ratios and 95% confidence intervals correspond to an IQR increase in pollutant value for each exposure window reported in Table 6.2

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ SGA counts aggregated by conception date, offset by total number of conceptions, Poisson models control for long term trends, seasonal trends, marital status, education

Ψ SGA counts aggregated at week 37 of gestation (day 259), offset by all gestations at 37 weeks gestation on given date, Poisson models control for long term trends, seasonal trends, marital status, education

‡ SGA counts aggregated by birth date, offset by total live births, Poisson models control for long term trends, seasonal trends, marital status, education.

Table 6.4. Risk ratios and 95% confidence intervals** for ambient air pollution levels in selected gestational windows and SGA for births with a maternal residential address within 4 miles of a monitor

	Full Term Births		Preterm Births			
Pollutant	First month of gestation ¥ RR (95% CI)	Weeks 28-36 of gestation Ψ RR (95% CI)	First month of gestation ¥ RR (95% CI)	Final 9 weeks of gestation ‡ RR (95% CI)	N monitors	Approximate births within 4 miles of a monitor §
1-hour max CO (ppm)	1.01 (0.98, 1.05)	1.01 (0.96, 1.06)	1.12 (1.02, 1.23)*	0.91 (0.78, 1.06)	3	61,333
1-hour max NO_2 (ppb)	1.00 (0.97, 1.03)	1.00 (0.96, 1.05)	1.05 (0.97, 1.14)	1.07 (0.95, 1.21)	4	65,310
1-hour max SO_2 (ppb)	0.99 (0.95, 1.02)	0.99 (0.95, 1.03)	1.07 (0.96, 1.20)	0.91 (0.81, 1.02)	3	44,659
8-hour max O_3 (ppb)	0.96 (0.84, 1.09)	1.01 (0.84, 1.22)	1.18 (0.81, 1.71)	1.03 (0.59, 1.81)	3	49,154
24-hour PM_{10} ($\mu g/m^3$)	0.94 (0.86, 1.03)	0.90 (0.79, 1.03)	1.27 (0.94, 1.70)	1.12 (0.72, 1.73)	2	23,455
24-hour $PM_{2.5}$ ($\mu g/m^3$)	1.02 (0.95, 1.09)	1.06 (0.95, 1.18)	1.13 (0.92, 1.38)	1.10 (0.81, 1.49)	6	51,389
24-hour $PM_{2.5-10}$ ($\mu g/m^3$)	1.01 (0.92, 1.11)	0.96 (0.86, 1.08)	1.34 (1.01, 1.78)*	1.35 (0.96, 1.89)	1	16,738
24-hour $PM_{2.5}$ sulfate ($\mu g/m^3$)	0.93 (0.81, 1.06)	0.99 (0.79, 1.25)	1.33 (0.86, 2.05)	0.78 (0.38, 1.60)	1	16,738
24-hour $PM_{2.5}$ nitrate ($\mu g/m^3$)	0.95 (0.80, 1.12)	0.93 (0.75, 1.17)	1.02 (0.61, 1.69)	0.84 (0.42, 1.67)	1	16,738
24-hour $PM_{2.5}$ total carbon ($\mu g/m^3$)	0.99 (0.91, 1.07)	0.97 (0.85, 1.11)	1.10 (0.86, 1.41)	1.58 (1.04, 2.39)*	1	16,738
24-hour $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	0.98 (0.90, 1.06)	1.01 (0.88, 1.16)	1.09 (0.86, 1.39)	1.61 (1.05, 2.47)*	1	16,738
24-hour $PM_{2.5}$ organic carbon ($\mu g/m^3$)	1.00 (0.92, 1.08)	0.97 (0.86, 1.08)	1.09 (0.85, 1.41)	1.41 (1.00, 1.98)	1	16,738
24-hour $PM_{2.5}$ water-soluble metals ($\mu g/m^3$) †	0.92 (0.79, 1.08)	1.00 (0.76, 1.32)	1.17 0.71, 1.93)	0.71 (0.32, 1.61)	1	16,738

* $p<0.05$

** Risk ratios and 95% confidence intervals correspond to an IQR increase in pollutant value for each exposure window reported in Table 6.2

§ Exact number of births analyzed differed slightly by exposure window and missing exposure assignments

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ SGA counts aggregated by conception date, offset by total number of conceptions, Poisson models control for long term trends, seasonal trends, marital status, education

Ψ SGA counts aggregated at week 37 of gestation (day 259), offset by all gestations at exactly 37 weeks on given date, Poisson models control for long term trends, seasonal trends, marital status, education

‡ SGA counts aggregated by birth date, offset by total live births, Poisson models control for long term trends, seasonal trends, marital status, education.

CHAPTER 7: Conclusion

In this dissertation, relationships between ambient air pollutants and the adverse pregnancy outcomes of preterm birth and intrauterine growth restriction (IUGR) were investigated in a cohort of approximately 500,000 infants delivered between 1994 and 2004 in the five-county Atlanta metropolitan area. Using a time-series approach, aggregated daily counts of preterm birth and small for gestational age (SGA), a proxy measure of IUGR, were examined in relation to ambient levels of carbon monoxide, nitrogen dioxide, sulfur dioxide, ozone, PM_{10}, $PM_{2.5}$ and speciated PM measurements during selected gestational windows of interest. Daily pollutant levels in five-county Atlanta were characterized using a population-weighted spatial average of air quality monitors in the study area. Ambient concentrations at individual monitors were also used to assign exposure in analyses limited to mothers with residential geocodes within four miles of each station. Air quality measurements available at the Aerosol Research Inhalation Epidemiology Study (ARIES) monitor in downtown Atlanta allowed for the examination of speciated particle components, which have been unavailable in previous studies.

The majority of previous investigations of the relationship between air pollution and adverse pregnancy outcomes utilized spatio-temporal contrasts of exposure, comparing pregnant women across both space and time. Residual confounding by spatially varying individual risk factors such as socioeconomic status, which can be difficult to quantify and adequately control, is a concern in these studies. The studies conducted in this dissertation complement the existing literature by utilizing a temporal analytic strategy in which comparisons are made across days instead of individuals. Even in the capture area analyses limited to women residing near air quality monitors, the purely temporal nature of the analysis was maintained. The temporal models used to test the study hypotheses addressed the potential for confounding introduced by the seasonal patterns of birth described in Chapter four. These methodological considerations for temporal studies of preterm birth can be applied to future temporal investigations of air pollution

levels, infections, allergen levels, pesticide application, water quality, meteorological factors and other seasonally varying exposures in relation to adverse pregnancy outcomes.

In the preterm birth study, most relationships examined were consistent with little or no association. However, three positive associations between ambient pollution levels and preterm birth were observed in the capture area analyses. Preterm birth was associated with NO_2 in the six weeks before birth, $PM_{2.5}$ sulfate in the week before birth, and $PM_{2.5}$ water-soluble metals in the week before birth. $PM_{2.5}$ sulfate and $PM_{2.5}$ water soluble metals have not been assessed previously in relation to preterm birth, and these associations should be confirmed in other populations. Of the three associations observed, the NO_2 association is the most compelling. Effect estimates were similar across three of the four individual NO_2 monitors examined, and traffic-related pollutants have been associated with preterm birth in previous investigations, although results specifically for NO_2 have been mixed. While the results of this study provided support for some of the secondary study hypotheses, there was little evidence to support the primary hypotheses.

The small for gestational age (SGA) study provided some evidence for early and late pregnancy effects of air pollution on reduced fetal growth, but only in the subset of infants born prematurely. In the capture area analyses, positive associations were observed between preterm SGA and CO and coarse PM levels in the first month of gestation, and carbonaceous $PM_{2.5}$ in the final nine weeks of pregnancy. Most previous studies have restricted analyses of fetal growth outcomes to full term infants. In this study, results were consistent with little or no association between ambient levels of air pollution and full term SGA for all pollutants and gestational windows investigated. Because of the morbidity and mortality observed in infants who are both small and preterm, the relationship between air pollution and reduced fetal growth in preterm infants could have important public health implications. Future investigations of air pollution and fetal growth should consider this potentially susceptible subpopulation. Like the preterm birth study, results of the SGA study provided support for some of the secondary study hypotheses but did not provide evidence to support the primary hypotheses.

Inconsistent results among the studies conducted to date may reflect differences in pollution levels and composition across locations, outcome definitions, exposure assessment, population characteristics and behaviors, or Type I errors resulting from multiple testing. In this dissertation, most of the relationships examined, including the all the primary hypotheses, were consistent with little or no association. These null results may indicate a lack of true association, or may be biased toward the null as a result of measurement error in the exposure and outcomes. The positive associations observed provide some support for an effect of ambient air pollution on preterm birth and fetal growth in infants born prematurely but should be interpreted with caution given the large number of gestational windows and pollutants investigated and lack of strong a priori evidence for the associations observed.

APPENDIX A

Additional analyses of seasonality of birth in Atlanta and implications for temporal studies of preterm birth

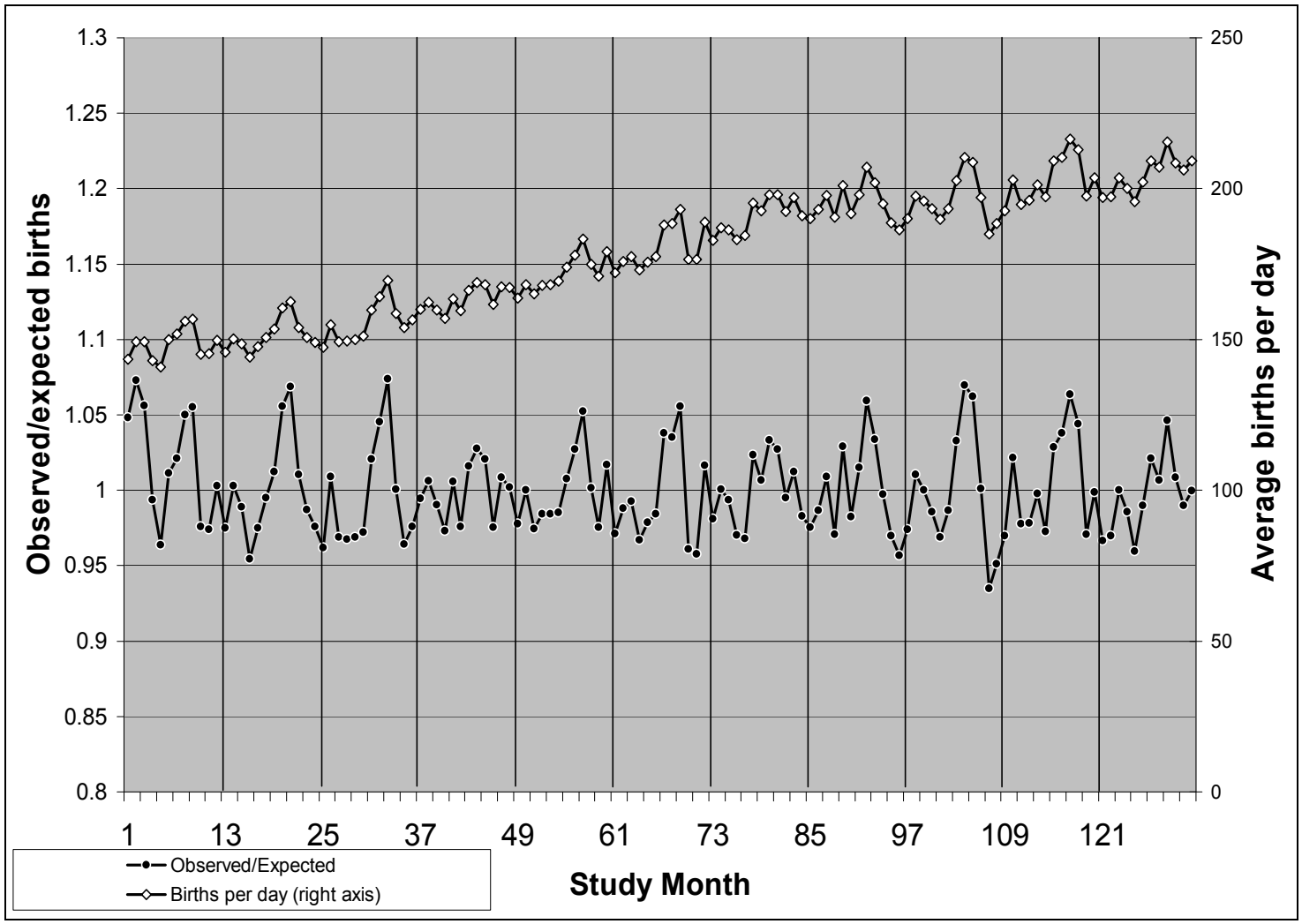


Figure A1. Average births per day by study month and observed/expected births by study month in the twenty-county Atlanta metropolitan area, expected births based on a 12-month moving average

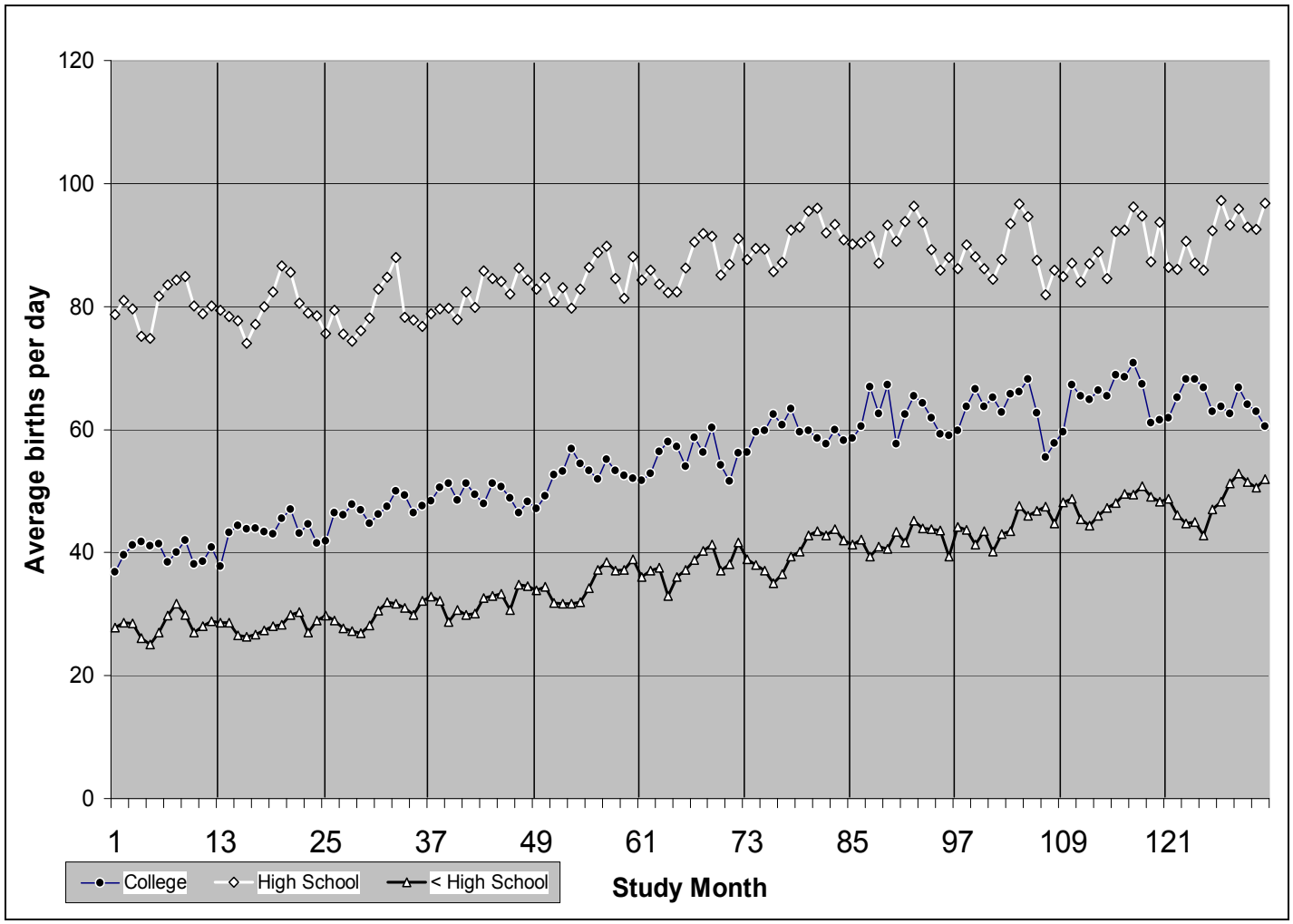


Figure A2. Average births per day by study month in the twenty-county Atlanta area stratified by maternal education

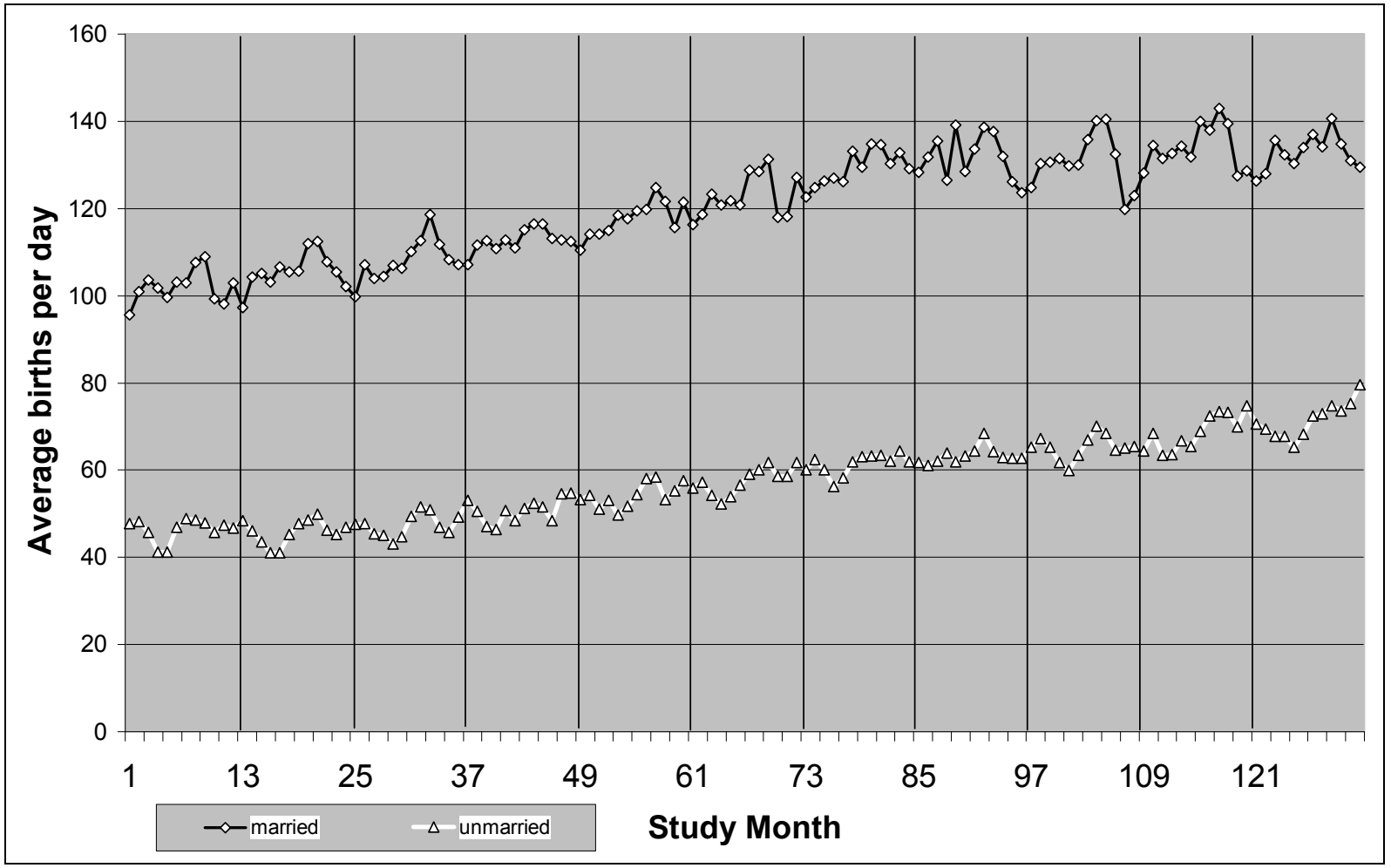


Figure A3. Average births per day by study month in the twenty-county Atlanta area stratified by marital status

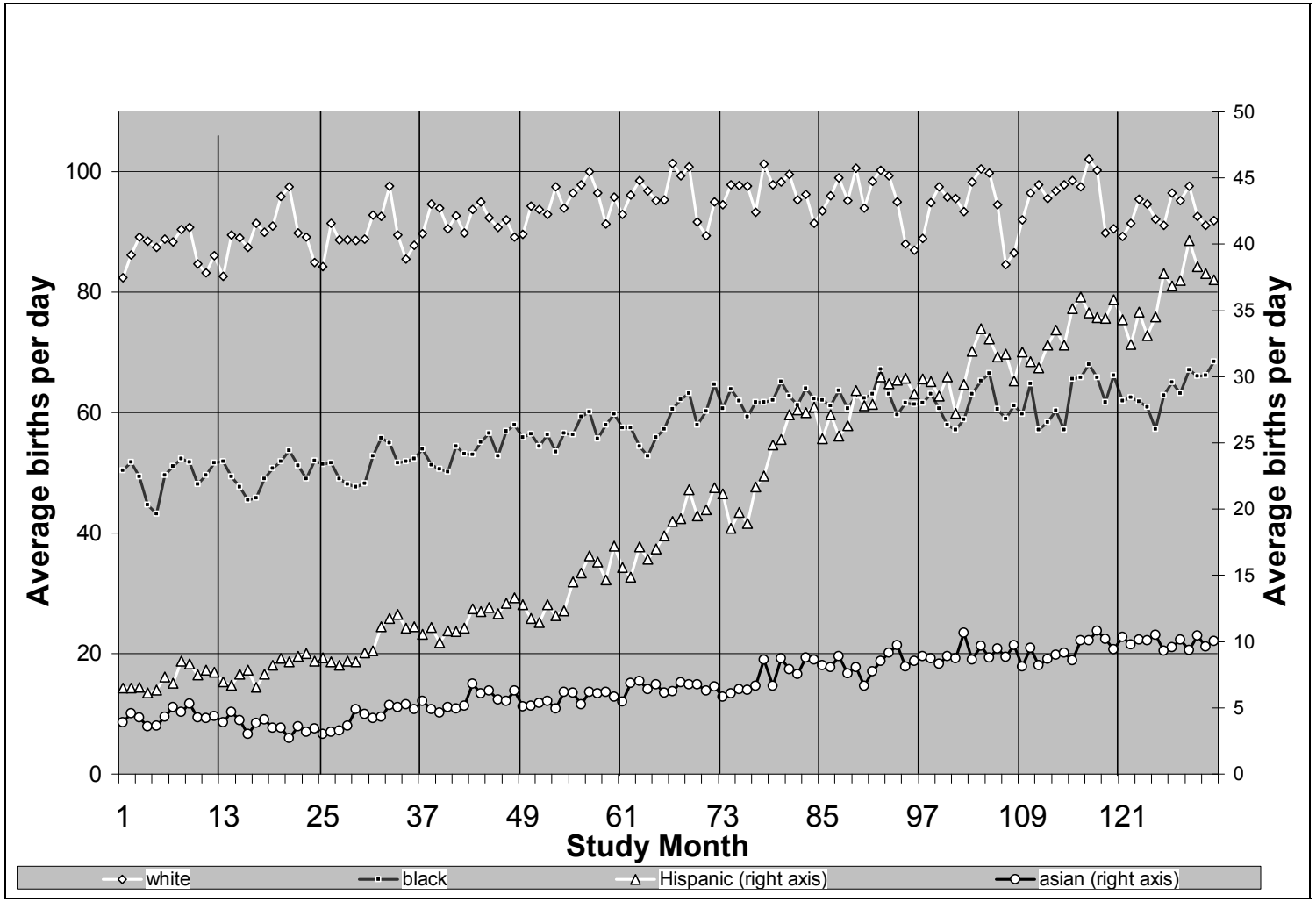


Figure A4. Average births per day by study month in the twenty-county Atlanta area stratified by maternal race/ethnicity

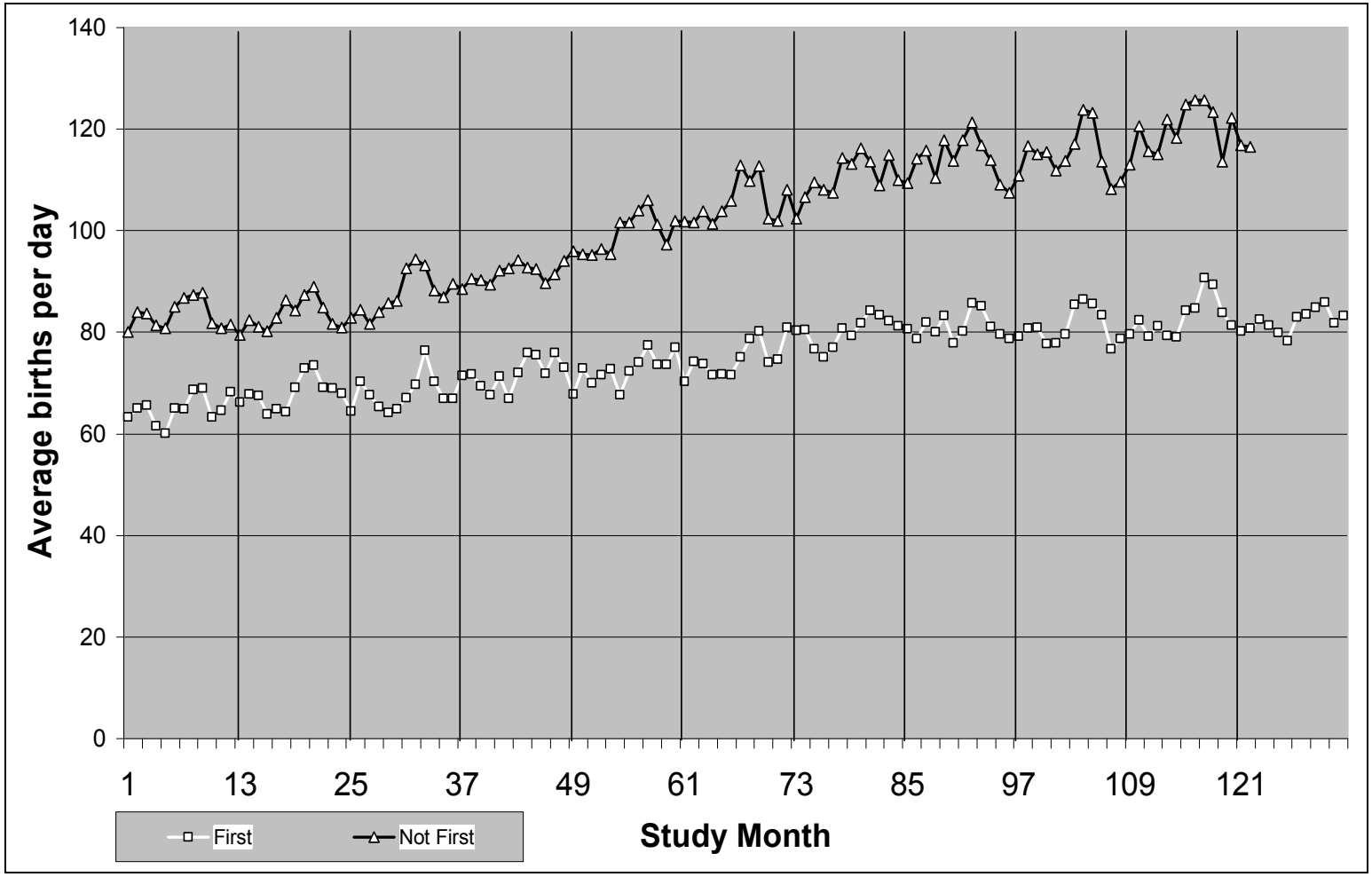


Figure A5. Average births per day by study month in the twenty-county Atlanta area stratified by firstborn status

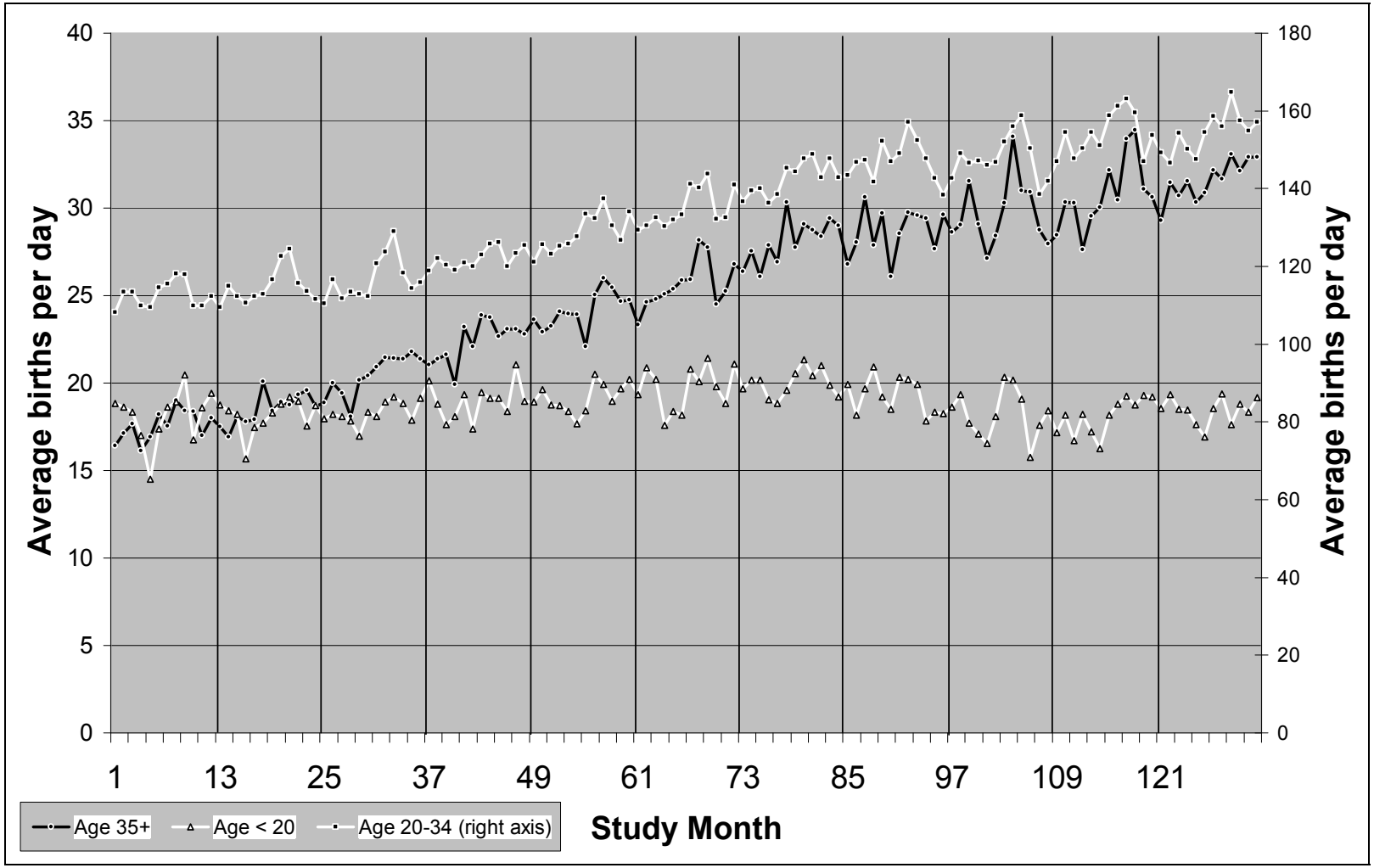


Figure A6. Average births per day by study month in the twenty-county Atlanta area stratified by maternal age group

Table A1. Crude risk ratios for preterm birth comparing socio-demographic groups at various gestational ages using the conditional probability of birth at each gestational age (conditioned on reaching the gestational age of interest).

Gestational Age	RR Black vs. White	RR Hisp vs. White	RR College vs. HS+	RR LTHS vs. HS+	RR Unmarried vs. Married
20	3.50	1.00	0.50	0.75	2.00
21	2.67	0.67	0.60	0.80	2.33
22	4.50	1.50	0.56	0.89	2.33
23	3.60	1.20	0.60	1.00	2.67
24	3.29	0.86	0.64	0.86	2.22
25	3.50	1.00	0.69	0.94	2.30
26	3.00	1.00	0.58	0.95	2.17
27	3.00	1.10	0.67	1.17	2.17
28	2.50	1.00	0.73	1.05	1.94
29	2.29	0.71	0.69	1.04	1.79
30	2.08	0.83	0.76	1.15	1.84
31	1.81	0.88	0.74	1.10	1.72
32	1.71	0.94	0.76	1.08	1.61
33	1.63	0.88	0.79	1.10	1.51
34	1.51	0.92	0.86	1.09	1.45
35	1.39	0.87	0.84	1.05	1.33
36	1.27	0.88	0.91	1.03	1.21

*College=16+ years education, HS+ =12-15 years education, LTHS=<12 years education

APPENDIX B

Additional analyses of ambient air pollution and preterm birth in Atlanta, 1994-2004: a time-series analysis

Table B1. Crude associations between air pollution in three gestational windows and preterm birth in five-county Atlanta, 1994-2004

	First month of gestation¥		Final 1 week of pregnancy‡		Final 6 weeks of pregnancy‡	
Pollutant	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
1-hr max CO (ppm)	0.9864 (0.9737-0.9992)	0.04	0.9872 (0.9740-1.0005)	0.06	0.9743 (0.9597-0.9891)	0.0007
1-hr max NO_2 (ppb)	0.9919 (0.9808-1.0032)	0.16	0.9912 (0.9779-1.0046)	0.20	0.9885 (0.9745-1.0027)	0.11
1-hr max SO_2 (ppb)	0.9892 (0.9775-1.0010)	0.07	0.9944 (0.9812-1.0078)	0.41	0.9846 (0.9727-0.9967)	0.01
8-hr max O_3 (ppb)	0.9873 (0.9726-1.0022)	0.09	0.9855 (0.9705-1.0006)	0.06	0.9932 (0.9758-1.0109)	0.45
24-hr PM_{10} (µg/m3)	0.9872 (0.9747-0.9999)	0.05	0.9854 (0.9718-0.9991)	0.04	0.9885 (0.9727-1.0046)	0.16
24-hr $PM_{2.5}$ (µg/m3)	0.9839 (0.9693-0.9988)	0.03	0.9788 (0.9640-0.9939)	0.01	0.9800 (0.9627-0.9975)	0.03
24-hr $PM_{2.5-10}$ (µg/m3)	0.9902 (0.9770-1.0036)	0.15	0.9872 (0.9720-1.0027)	0.11	0.9949 (0.9791-1.0109)	0.53
24-hr $PM_{2.5}$ SO_4 (µg/m3)	0.9901 (0.9738-1.0066)	0.24	0.9891 (0.9722-1.0063)	0.21	0.9878 (0.9669-1.0091)	0.26
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.9948 (0.9775-1.0124)	0.56	0.9928 (0.9751-1.0109)	0.43	0.9884 (0.9675-1.0096)	0.28
24-hr $PM_{2.5}$ OC (µg/m3)	0.9788 (0.9640-0.9939)	0.01	0.9907 (0.9748-1.0069)	0.26	0.9961 (0.9776-1.0150)	0.68
24-hr $PM_{2.5}$ EC (µg/m3)	0.9806 (0.9682-0.9932)	0.003	0.9933 (0.9799-1.0070)	0.34	0.9856 (0.9705-1.0009)	0.06
24-hr $PM_{2.5}$ TC (µg/m3)	0.9786 (0.9650-0.9923)	0.002	0.9906 (0.9751-1.0063)	0.24	0.9902 (0.9720-1.0088)	0.30
24-hr $PM_{2.5}$ WS metals† (µg/m3)	0.9968 (0.9777-1.0162)	0.74	0.9974 (0.9783-1.0168)	0.79	1.0060 (0.9852-1.0273)	0.57

* Risk ratios and 95% confidence intervals correspond to an IQR increase in the air pollutant value for each exposure window reported in Table 2
¥ Counts aggregated by conception date, offsetting by total conceptions
‡ Counts aggregated by birth date, offsetting by gestations at risk, extremely preterm births <29 weeks are excluded

Table B2. Risk ratios, 95% confidence intervals and p-values for spontaneous preterm birth in five-county Atlanta, 1994-2004 (induced preterm births excluded)

Pollutant	First month of gestation ¥ RR (95% CI)*	p	Final 1 week of pregnancy ‡ RR (95% CI)*	p	Final 6 weeks of pregnancy ‡ RR (95% CI)*	p
1-hr max CO (ppm)	1.0020 (0.9730-1.0318)	0.89	0.9986 (0.9797-1.0179)	0.89	0.9671 (0.9287-1.0070)	0.11
1-hr max NO_2 (ppb)	0.9898 (0.9746-1.0052)	0.19	0.9963 (0.9806-1.0123)	0.65	0.9940 (0.9734-1.0151)	0.57
1-hr max SO_2 (ppb)	0.9659 (0.9478-0.9844)	0.0003	0.9948 (0.9789-1.0110)	0.53	0.9861 (0.9660-1.0067)	0.18
8-hr max O_3 (ppb)	0.9596 (0.9180-1.0030)	0.07	0.9861 (0.9573-1.0156)	0.35	0.9865 (0.9293-1.0471)	0.65
24-hr PM_{10} (μg/m3)	0.9885 (0.9672-1.0102)	0.30	0.9855 (0.9675-1.0038)	0.12	0.9690 (0.9394-0.9996)	0.05
24-hr $PM_{2.5}$ (μg/m3)	1.0034 (0.9777-1.0299)	0.80	0.9832 (0.9629-1.0040)	0.11	0.9738 (0.9390-1.0098)	0.15
24-hr $PM_{2.5-10}$ (μg/m3)	0.9909 (0.9669-1.0155)	0.47	0.9874 (0.9674-1.0078)	0.22	1.0004 (0.9694-1.0325)	0.98
24-hr $PM_{2.5}$ SO_4 (μg/m3)	1.0042 (0.9684-1.0413)	0.82	0.9860 (0.9593-1.0134)	0.31	0.9314 (0.8784-0.9877)	0.02
24-hr $PM_{2.5}$ NO_3 (μg/m3)	1.0195 (0.9757-1.0653)	0.39	0.9834 (0.9547-1.0131)	0.27	0.9606 (0.9059-1.0185)	0.18
24-hr $PM_{2.5}$ OC (μg/m3)	0.9864 (0.9648-1.0085)	0.22	0.9870 (0.9678-1.0066)	0.19	0.9839 (0.9554-1.0132)	0.28
24-hr $PM_{2.5}$ EC (μg/m3)	0.9894 (0.9658-1.0135)	0.38	1.0013 (0.9827-1.0202)	0.89	0.9821 (0.9470-1.0185)	0.33
24-hr $PM_{2.5}$ TC (μg/m3)	0.9875 (0.9665-1.0090)	0.25	0.9911 (0.9719-1.0107)	0.37	0.9818 (0.9506-1.0140)	0.26
24-hr $PM_{2.5}$ WS metals† (μg/m3)	1.0085 (0.9665-1.0524)	0.70	0.9917 (0.9621-1.0223)	0.59	0.9489 (0.8876-1.0145)	0.12

*Risk ratios and 95% confidence intervals correspond to an IQR increase in the air pollutant value for each exposure window reported in Table 5.2

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ Counts aggregated by conception date, offsetting by total conceptions, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education

‡ Counts aggregated by birth date, offsetting by gestations at risk, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

To explore the possibility that the gestational window of vulnerability was mispecified, exposures during other potential gestational windows of susceptibility were systematically assessed in relation to preterm birth. In this analysis births were aggregated by conception date and the pollution assigned to each conception date in the time-series represented pollution levels in different months of gestation. Pollution levels in the month before each conception date were also assessed (month -1 of gestation). The analyses examining months 5, 6, 7, and 8 of gestation were limited to infants who reached at least 5 month, 6 months, 7 months or 8 months respectively.

Figure B1. Risk ratios and 95% confidence intervals for ambient levels of criteria pollutants in months -1 through 8 of gestation and preterm birth, for births in five-county Atlanta, 1994-2004

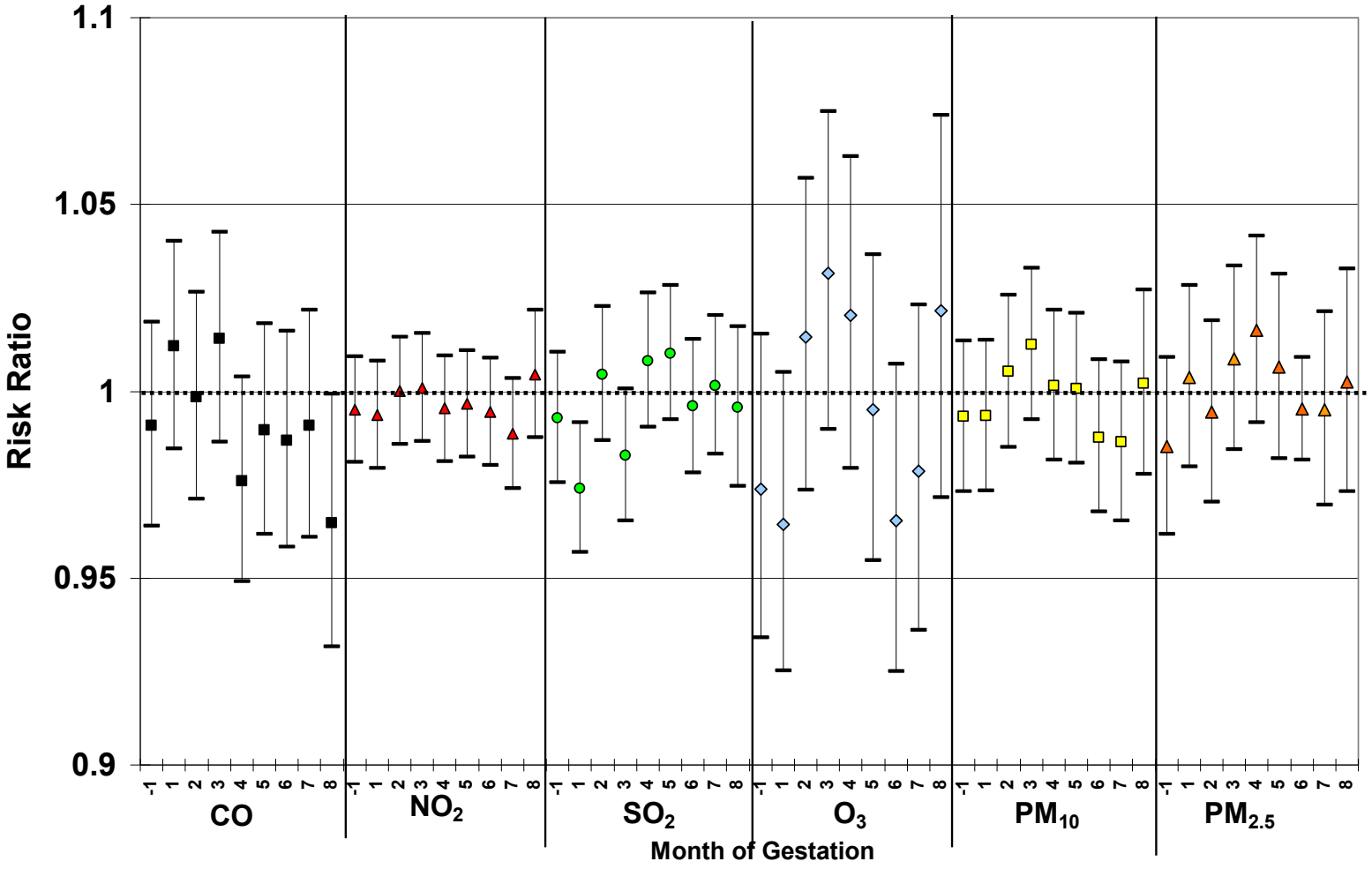
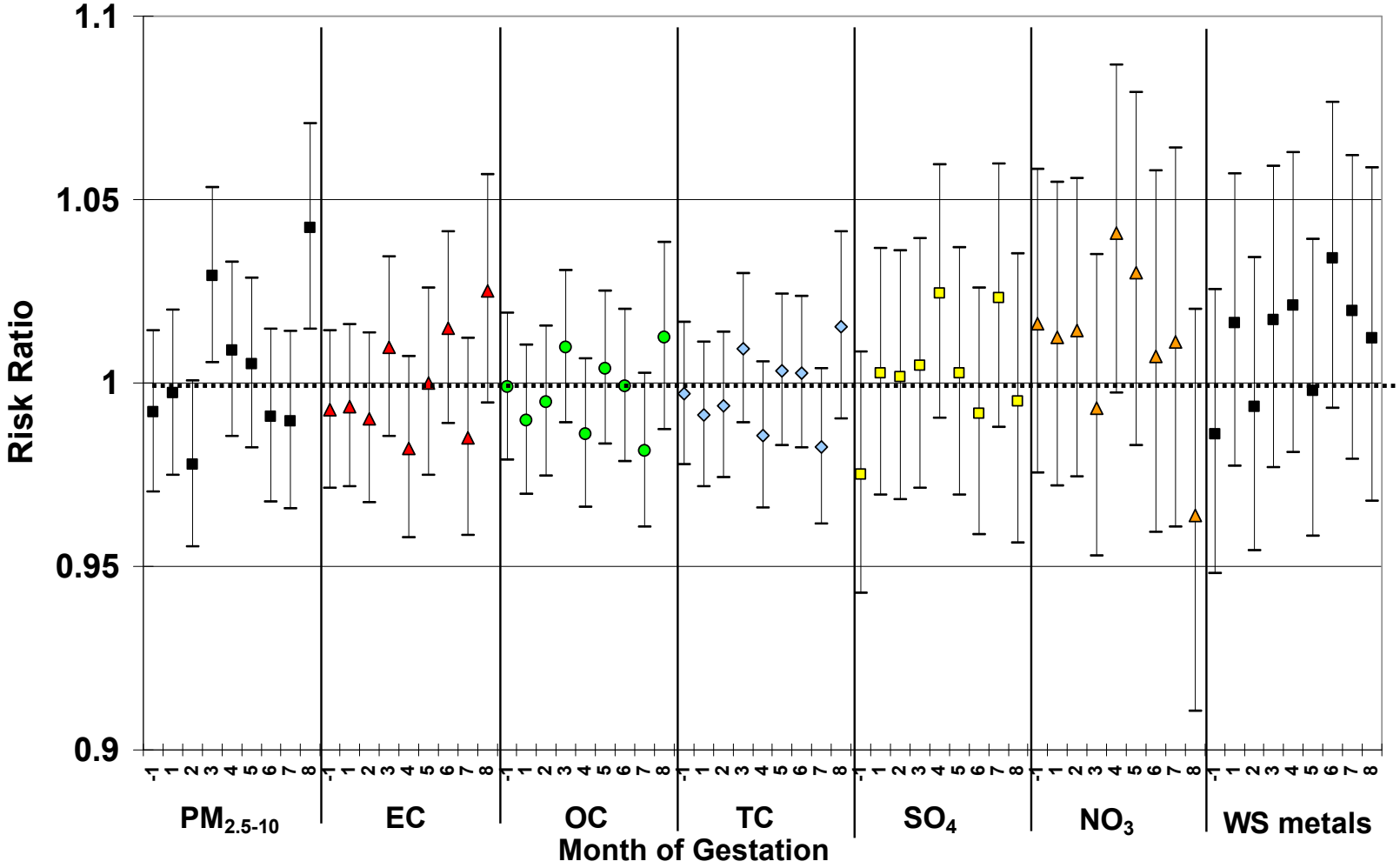


Figure B2. Risk ratios and 95% confidence intervals for ambient levels of PM components in months -1 through 8 of gestation and preterm birth, for births in five-county Atlanta, 1994-2004



We also examined average pollution levels in the 8-14 days before birth and the 15-21 days before birth, aggregating by birth date and offsetting by the number of gestations at risk.

Table B3. Risk ratios, 95% confidence intervals* and p-values for ambient levels air pollution in the week before birth, the 8-14 days before birth and the 15-21 days before birth and preterm birth, for births in five-county Atlanta, 1994-2004

		1 week before birth (lag0-7)‡		2 weeks before birth (lag 8-14)		3 weeks before birth (lag 15-21)	
Pollutant	**Unit**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
1-hour max CO (ppm)	0.37	0.9991 (0.9813-1.0172)	0.92	0.9961 (0.9784-1.0142)	0.67	0.9924 (0.9747-1.0103)	0.40
1-hour max NO2 (ppb)	8	0.9952 (0.9806-1.0100)	0.52	1.0080 (0.9933-1.0230)	0.29	1.0036 (0.9889-1.0185)	0.63
1-hour max SO2 (ppb)	6	0.9945 (0.9796-1.0096)	0.47	1.0034 (0.9884-1.0186)	0.66	1.0002 (0.9852-1.0153)	0.98
8-hour max O3 (ppb)	25	0.9861 (0.9594-1.0136)	0.32	1.0203 (0.9924-1.0489)	0.16	1.0068 (0.9794-1.0349)	0.63
24-hour PM10 (μg/m3)	10	0.9862 (0.9695-1.0032)	0.11	0.9987 (0.9818-1.0160)	0.89	1.0046 (0.9877-1.0218)	0.59
24-hour PM2.5 (μg/m3)	6	0.9840 (0.9653-1.0031)	0.10	0.9988 (0.9799-1.0181)	0.90	0.9977 (0.9789-1.0168)	0.81
24-hour PM2.5-10 (μg/m3)	3.6	0.9918 (0.9730-1.0110)	0.40	1.0082 (0.9892-1.0275)	0.40	1.0041 (0.9852-1.0232)	0.68
24-hour PM2.5 SO4 (μg/m3)	3.0	0.9819 (0.9574-1.0070)	0.16	0.9885 (0.9640-1.0135)	0.36	0.9944 (0.9700-1.0195)	0.66
24-hour PM2.5 NO3 (μg/m3)	0.75	0.9872 (0.9606-1.0146)	0.36	0.9877 (0.9613-1.0148)	0.37	0.9975 (0.9708-1.0248)	0.85
24-hour PM2.5 OC (μg/m3)	1.7	0.9867 (0.9690-1.0047)	0.15	0.9962 (0.9786-1.0140)	0.67	0.9975 (0.9799-1.0154)	0.78
24-hour PM2.5 EC (μg/m3)	0.70	0.9980 (0.9809-1.0154)	0.82	0.9990 (0.9821-1.0162)	0.91	1.0032 (0.9867-1.0199)	0.71
24-hour PM2.5 TC (μg/m3)	2.3	0.9896 (0.9719-1.0076)	0.26	0.9966 (0.9791-1.0144)	0.71	0.9989 (0.9815-1.0166)	0.90
24-hour PM2.5 WS metals (μg/m3)	0.020	0.9848 (0.9576-1.0127)	0.28	0.9882 (0.9616-1.0154)	0.39	0.9920 (0.9661-1.0185)	0.55

‡ Results from the final model for the 1 week exposure window
*Risk ratios and 95% confidence intervals correspond to an IQR increase in the air pollutant value for each exposure window reported in Table 5.2
Counts aggregated by birth date, offsetting by gestations at risk, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.
† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B4. Season-specific* risk ratios and p-values for air pollution in the first month of gestation and preterm birth in five-county Atlanta, 1994-2004.

	FALL		WINTER		SPRING		SUMMER	
Pollutant	**RR****	**p**	**RR****	**p**	**RR****	**p**	**RR****	**p**
1-hr max CO (ppm)	0.9998	0.99	1.0132	0.61	1.0565	0.20	0.9972	0.92
1-hr max NO_2 (ppb)	0.9953	0.72	0.9231	<0.0001	1.0216	0.23	0.9973	0.85
1-hr max SO_2 (ppb)	0.9718	0.04	0.9732	0.09	0.9815	0.30	1.011	0.58
8-hr max O_3 (ppb)	1.0327	0.20	0.9693	0.45	0.9248	0.02	0.9921	0.81
24-hr PM_{10} (µg/m3)	1.0147	0.31	0.9774	0.51	0.9641	0.13	0.9886	0.57
24-hr $PM_{2.5}$ (µg/m3)	1.0165	0.32	0.9577	0.31	0.9712	0.39	0.9982	0.93
24-hr $PM_{2.5-10}$ (µg/m3)	0.9931	0.69	1.0068	0.80	1.0114	0.61	0.9675	0.50
24-hr $PM_{2.5}$ SO_4 (µg/m3)	1.0168	0.49	1.0393	0.65	0.9506	0.28	0.9956	0.86
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.9854	0.57	1.0205	0.48	1.0642	0.08	0.9679	0.74
24-hr $PM_{2.5}$ OC (µg/m3)	0.9932	0.59	0.9459	0.005	0.9843	0.61	0.9888	0.70
24-hr $PM_{2.5}$ EC (µg/m3)	0.9902	0.45	0.9885	0.61	1.0029	0.95	0.9906	0.80
24-hr $PM_{2.5}$ TC (µg/m3)	0.9928	0.55	0.9523	0.02	0.987	0.69	0.9895	0.72
24-hr $PM_{2.5}$ WS metals† (µg/m3)	0.9904	0.70	1.1762	0.04	0.981	0.65	1.0012	0.98

* Fall: Sept-Nov Winter: Dec-Feb Spring: Mar-May Summer: June-August
**Risk ratios correspond to an IQR increase for the 4 week pollution average reported in Table 5.2
Counts are aggregated by conception date, offsetting by total conceptions, Poisson models control for year, maternal race/ethnicity, marital status, education
† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B5. Season-specific* risk ratios and p-values for air pollution in the last week of gestation and preterm birth in five-county Atlanta, 1994-2004.

	FALL		WINTER		SPRING		SUMMER	
Pollutant	**RR****	**p**	**RR****	**p**	**RR****	**p**	**RR****	**p**
1-hr max CO (ppm)	0.9748	0.09	1.0218	0.12	1.0347	0.17	0.9581	0.11
1-hr max NO_2 (ppb)	0.9894	0.39	1.0302	0.08	0.99	0.55	0.9767	0.12
1-hr max SO_2 (ppb)	0.9869	0.35	1.0095	0.47	0.9885	0.49	0.9847	0.33
8-hr max O_3 (ppb)	0.9860	0.45	0.9778	0.63	1.0174	0.49	0.9721	0.19
24-hr PM_{10} (µg/m3)	0.9777	0.08	1.0228	0.33	1.0191	0.38	0.9815	0.23
24-hr $PM_{2.5}$ (µg/m3)	0.9803	0.17	0.9898	0.71	1.0057	0.84	0.9786	0.19
24-hr $PM_{2.5-10}$ (µg/m3)	0.9912	0.54	1.0135	0.60	1.0010	0.96	0.9708	0.23
24-hr $PM_{2.5}$ SO_4 (µg/m3)	0.9863	0.45	1.0513	0.47	1.0191	0.56	0.9811	0.28
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.9742	0.30	0.9974	0.89	0.9798	0.42	1.0504	0.52
24-hr $PM_{2.5}$ OC (µg/m3)	0.9828	0.17	1.0092	0.58	0.9976	0.92	0.9586	0.08
24-hr $PM_{2.5}$ EC (µg/m3)	0.9938	0.57	1.0158	0.36	0.9970	0.91	0.9782	0.41
24-hr $PM_{2.5}$ TC (µg/m3)	0.9850	0.22	1.0117	0.49	0.9973	0.92	0.9621	0.11
24-hr $PM_{2.5}$ WS metals† (µg/m3)	1.0115	0.55	1.0154	0.76	1.0219	0.48	0.9545	0.07

* Fall: Sept-Nov Winter: Dec-Feb Spring: Mar-May Summer: June-August

**Risk ratios correspond to an IQR increase for the 1 week pollution average reported in Table 5.2

Counts aggregated by birth date, offsetting by gestations at risk, Poisson models control for year, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B6. Season-specific* risk ratios and p-values for air pollution in the final six weeks of gestation and preterm birth in five-county Atlanta, 1994-2004.

	FALL		WINTER		SPRING		SUMMER	
Pollutant	**RR****	**p**	**RR****	**p**	**RR****	**p**	**RR****	**p**
1-hr max CO (ppm)	0.9559	0.09	1.0042	0.89	1.0217	0.64	1.0375	0.51
1-hr max NO_2 (ppb)	0.9896	0.51	1.0324	0.20	0.9979	0.93	1.0306	0.16
1-hr max SO_2 (ppb)	0.9680	0.07	0.9920	0.69	0.9965	0.83	0.9760	0.26
8-hr max O_3 (ppb)	1.0103	0.64	1.0249	0.79	1.0307	0.35	1.0050	0.92
24-hr PM_{10} (µg/m3)	0.9726	0.19	1.0329	0.23	1.0613	0.06	0.9966	0.90
24-hr $PM_{2.5}$ (µg/m3)	0.9679	0.14	1.0480	0.21	1.0646	0.23	0.9807	0.49
24-hr $PM_{2.5-10}$ (µg/m3)	0.9824	0.53	1.0304	0.17	1.0334	0.14	1.0031	0.95
24-hr $PM_{2.5}$ SO_4 (µg/m3)	0.9819	0.36	1.0591	0.65	0.9891	0.89	0.9629	0.36
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.9340	0.09	0.9913	0.76	1.0048	0.88	0.9796	0.86
24-hr $PM_{2.5}$ OC (µg/m3)	0.9751	0.13	1.0305	0.15	1.0112	0.75	0.9959	0.93
24-hr $PM_{2.5}$ EC (µg/m3)	0.9717	0.15	1.0238	0.38	0.9890	0.80	1.0081	0.92
24-hr $PM_{2.5}$ TC (µg/m3)	0.9737	0.13	1.0306	0.18	1.0070	0.86	0.9975	0.96
24-hr $PM_{2.5}$ WS metals† (µg/m3)	0.9817	0.54	1.0817	0.34	0.9780	0.75	0.9891	0.84

* Fall: Sept-Nov Winter: Dec-Feb Spring: Mar-May Summer: June-August

**Risk ratios correspond to an IQR increase for the 6 week pollution average reported in Table 5.2

Counts aggregated by birth date, offsetting by gestations at risk, Poisson models control for year, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B7. Risk ratios, 95% confidence intervals and p-values for air pollution in the first month of gestation and preterm birth using alternative approaches of temporal control

		FINAL MODEL -Day of study spline with 1 knot/yr -Day of year spline with 1 knot/month		**CONDITIONAL POISSON** -Day of study spline with 1 knot/yr -Indicator variables for week of year (matched on week of year)		**TEMP+INDICATOR** -Year indicator variables - 4 seasonal indicator variables - control for temperature and dew point temperature in the first month of gestation		**TEMP+SPLINE** - Day of study spline with 2 knots/year (apr and oct) - control for temperature and dew point temperature in the first month of gestation	
Pollutant	**Unit**	**RR 95% CI**	**p**	**RR 95% CI**	**p**	**RR 95% CI**	**p**	**RR 95% CI**	**p**
1-hr max CO (ppm)	0.32	1.0125 0.9851 1.0406	0.37	1.0114 0.9838 1.0397	0.42	0.9966 0.9738 1.0199	0.77	1.0181 0.9922 1.0446	0.17
1-hr max NO_2 (ppb)	5	0.9935 0.9793 1.0079	0.38	0.9922 0.9779 1.0066	0.29	0.9910 0.9747 1.0075	0.28	1.0016 0.9849 1.0185	0.86
1-hr max SO_2 (ppb)	4	0.9742 0.9571 0.9916	0.004	0.9746 0.9573 0.9922	0.005	0.9878 0.9708 1.0050	0.16	0.9761 0.9593 0.9933	0.01
8-hr max O_3 (ppb)	25	0.9613 0.9223 1.0020	0.06	0.9601 0.9210 1.0010	0.06	0.9778 0.9334 1.0244	0.34	0.9334 0.8888 0.9804	0.01
24-hr PM_{10} (µg/m3)	8	0.9944 0.9747 1.0146	0.59	0.9916 0.9716 1.0120	0.42	1.0000 0.9793 1.0211	1.00	0.9894 0.9672 1.0121	0.36
24-hr $PM_{2.5}$ (µg/m3)	5	1.0033 0.9794 1.0278	0.79	0.9996 0.9756 1.0242	0.97	1.0003 0.9778 1.0234	0.98	0.9837 0.9600 1.0080	0.19
24-hr $PM_{2.5-10}$ (µg/m3)	2.7	0.9966 0.9743 1.0195	0.77	0.9939 0.9715 1.0168	0.60	0.9952 0.9738 1.0171	0.67	1.0116 (0.9918 1.0317	0.25
24-hr $PM_{2.5}$ EC (µg/m3)	0.53	0.9933 0.9716 1.0156	0.55	0.9904 0.9681 1.0133	0.41	0.9871 0.9675 1.0071	0.20	0.9968 0.9766 1.0174	0.76
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.66	1.0121 0.9717 1.0542	0.56	1.0128 0.9719 1.0555	0.55	1.0227 0.9846 1.0623	0.25	0.9866 0.9451 1.0300	0.54
24-hr $PM_{2.5}$ OC (µg/m3)	1.2	0.9897 0.9696 1.0102	0.32	0.9852 0.9650 1.0058	0.16	0.9808 0.9626 0.9994	0.04	0.9928 0.9740 1.0119	0.46
24-hr $PM_{2.5}$ SO_4 (µg/m3)	2.8	1.0009 0.9681 1.0348	0.96	0.9990 0.9656 1.0336	0.95	0.9932 0.9627 1.0247	0.67	0.9785 0.9476 1.0104	0.18
24-hr $PM_{2.5}$ TC (µg/m3)	1.6	0.9911 0.9716 1.0110	0.38	0.9870 0.9672 1.0071	0.20	0.9822 0.9643 1.0005	0.06	0.9942 0.9762 1.0126	0.54
24-hr $PM_{2.5}$ WS metals† (µg/m3)	0.017	1.0115 0.9727 1.0519	0.57	1.0066 0.9664 1.0485	0.75	0.9930 0.9592 1.0280	0.69	0.9967 0.9575 1.0375	0.87

Counts are aggregated by conception date, offsetting by total conceptions, all models control for maternal race/ethnicity, marital status, education

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B8. Risk ratios, 95% confidence intervals and p-values for air pollution in the final week of gestation and preterm birth using alternative approaches of temporal control

		FINAL MODEL -Day of study spline with 1 knot/yr -Day of year spline with 1 knot/month		**CONDITIONAL POISSON** -Day of study spline with 1 knot/yr -Indicator variables for week of year (matched on week of yr)		**TEMP+INDICATOR+SPLINE** -Month indicator variables -Day of study spline 1 knot/yr -Control for temperature and dew point temperature in the final week of gestation		**TEMP+SPLINE** -Day of study spline with 4 knots every year (Mar, Jun, Sep, Dec) - control for temperature and dew point temperature in the final week of gestation	
Pollutant	**Unit**	**RR 95% CI**	**p**	**RR 95% CI**	**p**	**RR 95% CI**	**p**	**RR 95% CI**	**p**
1-hr max CO (ppm)	0.37	0.9991 0.9813 1.0172	0.92	0.9972 0.9791 1.0156	0.76	0.9988 0.9800 1.0179	0.90	0.9988 0.9789 1.0192	0.91
1-hr max NO_2 (ppb)	8	0.9952 0.9806 1.0100	0.52	0.9939 0.9790 1.0090	0.43	1.0004 0.9825 1.0187	0.97	0.9985 0.9796 1.0177	0.87
1-hr max SO_2 (ppb)	6	0.9945 0.9796 1.0096	0.474	0.9914 0.9762 1.0068	0.270	0.9991 0.9828 1.0156	0.91	0.9962 0.9798 1.0129	0.66
8-hr max O_3 (ppb)	25	0.9861 0.9594 1.0136	0.32	0.9942 0.9664 1.0227	0.69	0.9965 0.9879 1.0052	0.43	0.9854 0.9483 1.0239	0.45
24-hr PM_{10} (µg/m3)	10	0.9862 0.9695 1.0032	0.11	0.9842 0.9672 1.0015	0.07	0.9846 0.9659 1.0037	0.11	0.9869 0.9669 1.0074	0.21
24-hr $PM_{2.5}$ (µg/m3)	6	0.9840 0.9653 1.0031	0.10	0.9856 0.9657 1.0059	0.16	0.9856 0.9658 1.0057	0.16	0.9836 0.9630 1.0047	0.13
24-hr $PM_{2.5\text{-}10}$ (µg/m3)	3.6	0.9918 0.9730 1.0110	0.40	0.9968 0.9765 1.0176	0.76	0.9896 0.9684 1.0112	0.34	0.9886 0.9675 1.0102	0.30
24-hr $PM_{2.5}$ EC (µg/m3)	0.70	0.9980 0.9809 1.0154	0.82	0.9988 0.9786 1.0195	0.91	0.9990 0.9814 1.0169	0.91	1.0006 0.9830 1.0186	0.95
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.75	0.9872 0.9606 1.0146	0.36	0.9824 0.9534 1.0123	0.25	0.9956 0.9658 1.0263	0.78	0.9979 0.9675 1.0292	0.89
24-hr $PM_{2.5}$ OC (µg/m3)	1.7	0.9867 0.9690 1.0047	0.15	0.9904 0.9716 1.0095	0.32	0.9815 0.9617 1.0017	0.07	0.9828 0.9627 1.0033	0.10
24-hr $PM_{2.5}$ SO_4 (µg/m3)	3.0	0.9819 0.9574 1.0070	0.16	0.9906 0.9647 1.0172	0.49	0.9823 0.9571 1.0082	0.18	0.9817 0.9555 1.0086	0.18
24-hr $PM_{2.5}$ TC (µg/m3)	2.3	0.9896 0.9719 1.0076	0.26	0.9927 0.9737 1.0121	0.46	0.9867 0.9672 1.0066	0.19	0.9878 0.9681 1.0078	0.23
24-hr $PM_{2.5}$ WS metals† (µg/m3)	0.020	0.9848 0.9576 1.0127	0.28	0.9858 0.9562 1.0162	0.36	0.9847 0.9570 1.0131	0.29	0.9896 0.9603 1.0197	0.49

Counts aggregated by birth date, offsetting by gestations at risk, extremely preterm births <29 weeks are excluded.
All models control for maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics.
† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B9. Risk ratios, 95% confidence intervals and p-values for air pollution in the final six weeks of gestation and preterm birth using alternative approaches of temporal control

		FINAL MODEL -Day of study spline with 1 knot/yr -Day of year spline with 1 knot/month		**CONDITIONAL POISSON** -Day of study spline with 1 knot/yr -Indicator variables for week of year (matched on week of year)		**TEMP+INDICATOR** -Year indicator variables - 4 seasonal indicator variables - Control for temperature and dew point temperature in the final 6 weeks of gestation		**TEMP+SPLINE** - Day of study spline with 2 knots/year (apr and oct) - Control for temperature and dew point temperature in the final 6 weeks of gestation	
Pollutant	**Unit**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
1-hr max CO (ppm)	0.3	0.9726 0.9365 1.0101	0.15	0.9740 0.9375 1.0119	0.18	0.9792 0.9496 1.0097	0.18	0.9875 (0.9538 1.0223)	0.48
1-hr max NO_2 (ppb)	5	1.0020 0.9826 1.0218	0.84	1.0011 0.9816 1.0211	0.91	1.0123 0.9906 1.0344	0.27	1.0147 (0.9910 1.0388)	0.23
1-hr max SO_2 (ppb)	3	0.9909 0.9720 1.0103	0.356	0.9880 0.9689 1.0074	0.224	0.9800 (0.9632 0.9971)	0.02	0.9785 (0.9607 0.9967)	0.02
8-hr max O_3 (ppb)	25	1.0037 0.9492 1.0614	0.90	1.0095 0.9541 1.0681	0.74	1.0528 0.9968 1.1120	0.07	1.0505 (0.9855 1.1198)	0.13
24-hr PM_{10} (µg/m3)	8	0.9823 0.9544 1.0110	0.22	0.9804 0.9522 1.0094	0.18	0.9918 0.9642 1.0202	0.57	0.9932 (0.9617 1.0257)	0.68
24-hr $PM_{2.5}$ (µg/m3)	5	0.9871 0.9546 1.0206	0.45	0.9870 0.9539 1.0214	0.45	0.9858 0.9569 1.0156	0.35	0.9834 (0.9514 1.0165)	0.32
24-hr $PM_{2.5-10}$ (µg/m3)	2.5	1.0124 0.9834 1.0424	0.41	1.0141 0.9848 1.0442	0.35	1.0204 0.9926 1.0489	0.15	1.0178 (0.9922 1.0440)	0.18
24-hr $PM_{2.5}$ EC (µg/m3)	0.55	1.0046 0.9714 1.0389	0.97	1.0078 0.9728 1.0440	0.67	0.9955 0.9680 1.0237	0.75	0.9957 (0.9666 1.0257)	0.78
24-hr $PM_{2.5}$ NO_3 (µg/m3)	0.64	0.9839 0.9321 1.0385	0.56	0.9832 0.9282 1.0414	0.56	0.9834 0.9378 1.0312	0.49	0.9767 (0.9182 1.0389)	0.45
24-hr $PM_{2.5}$ OC (µg/m3)	1.2	0.9956 0.9690 1.0228	0.75	0.9985 0.9704 1.0275	0.92	0.9978 0.9760 1.0200	0.84	0.9932 (0.9688 1.0181)	0.59
24-hr $PM_{2.5}$ SO_4 (µg/m3)	2.8	0.9455 0.8960 0.9978	0.04	0.9427 0.8910 0.9974	0.04	0.9545 0.9120 0.9990	0.05	0.9518 (0.9065 0.9993)	0.05
24-hr $PM_{2.5}$ TC (µg/m3)	1.7	0.9974 0.9681 1.0275	0.86	1.0006 0.9701 1.0321	0.97	0.9970 0.9733 1.0213	0.81	0.9934 (0.9673 1.0201)	0.62
24-hr $PM_{2.5}$ WS metals† (µg/m3)	0.016	0.9648 0.9072 1.0262	0.26	0.9597 0.8974 1.0263	0.23	0.9745 0.9261 1.0255	0.32	0.9668 (0.9052 1.0325)	0.31

Counts aggregated by birth date, offsetting by gestations at risk, extremely preterm births <29 weeks are excluded.
All models control for maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics.
† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

Table B10. Risk ratios, 95% confidence intervals and p-values for air pollution from a central monitor, as opposed to a population-weighted spatial average, and preterm birth in five-county Atlanta, 1994-2004

	First month of gestation¥		Final 1 week of pregnancy‡		Final 6 weeks of pregnancy‡	
Pollutant	**RR (95% CI)***	**p**	**RR (95% CI)***	**p**	**RR (95% CI)***	**p**
1-hr max CO (ppm)	1.0025 (0.9902-1.0149)	0.70	1.0003 (0.9926-1.0081)	0.94	1.0030 (0.9860-1.0204)	0.73
1-hr max NO_2 (ppb)	0.9962 (0.9876-1.0048)	0.39	0.9993 (0.9909-1.0077)	0.86	0.9988 (0.9868-1.0110)	0.85
1-hr max SO_2 (ppb)	0.9830 (0.9725-0.9935)	0.002	0.9982 (0.9893-1.0073)	0.70	0.9967 (0.9854-1.0081)	0.57
24-hr PM_{10} (µg/m3)	0.9937 (0.9741-1.0136)	0.53	0.9870 (0.9708-1.0036)	0.12	0.9851 (0.9573-1.0136)	0.30
24-hr $PM_{2.5}$ (µg/m3)	1.0042 (0.9796-1.0295)	0.74	0.9860 (0.9688-1.0036)	0.12	1.0083 (0.9722-1.0456)	0.66

*Risk ratios correspond to an IQR increase for the window-specific pollution average reported in Table 2
**O3 not included because central monitor did not monitor in winter
¥ Counts aggregated by conception date, offsetting by total conceptions, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education
‡ Counts aggregated by birth date, offsetting by gestations at risk, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

Analyses stratified by gestational week were conducted to explore the possibility that the effect of air pollution varies by degree of prematurity. Some risk factors for preterm birth are stronger for earlier or later preterm birth (e.g., 34-36), so it is possible that air pollution exposures exhibit a similar heterogeneity of effect.

Figure B3. Risk ratios and 95% confidence intervals for air pollution in the final week of gestation and preterm birth at specific gestational ages, for births in five-county Atlanta, 1994-2004

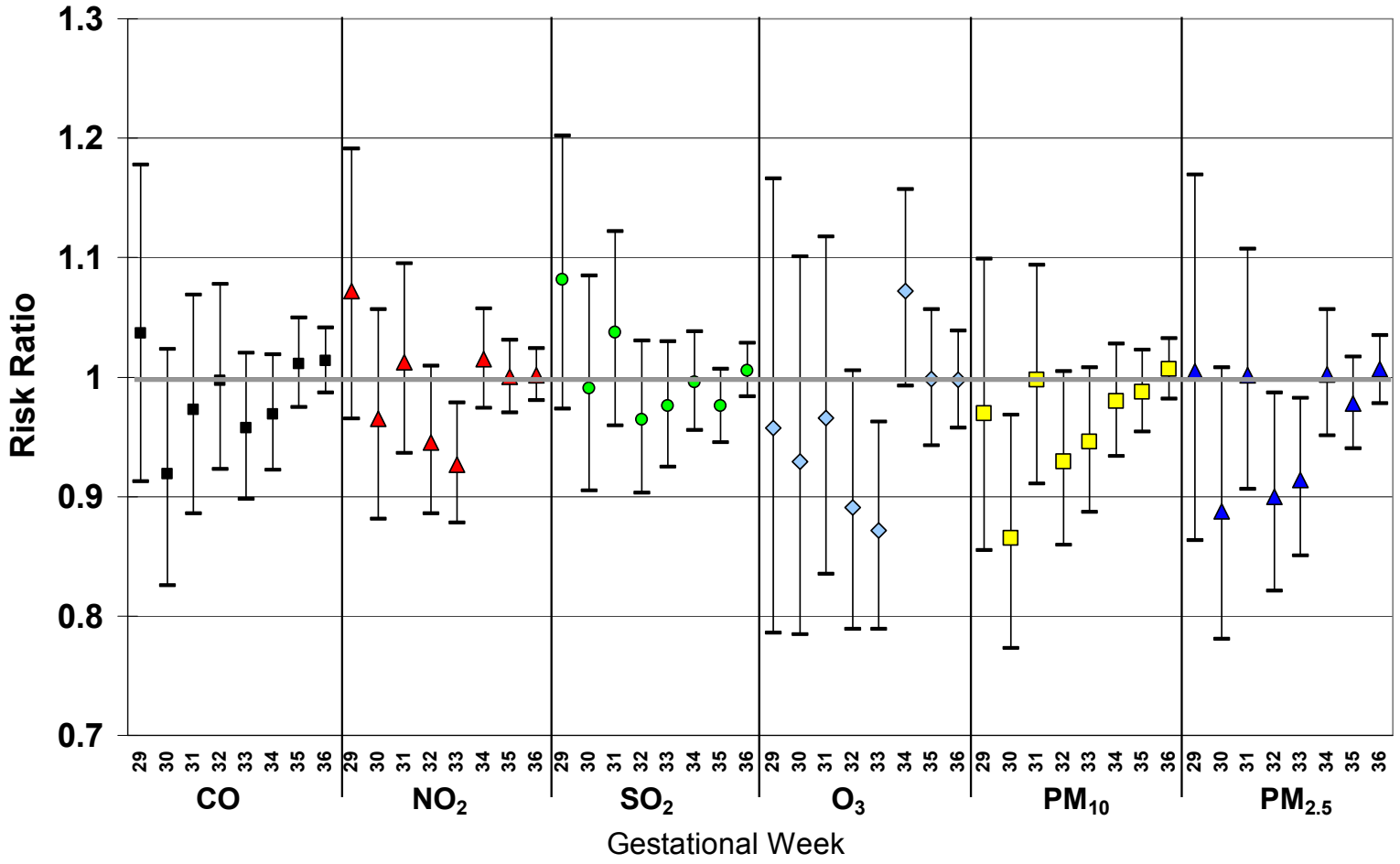


Figure B4. Risk ratios and 95% confidence intervals for air pollution in the final six week of gestation and preterm birth at specific gestational ages, for births in five-county Atlanta, 1994-2004

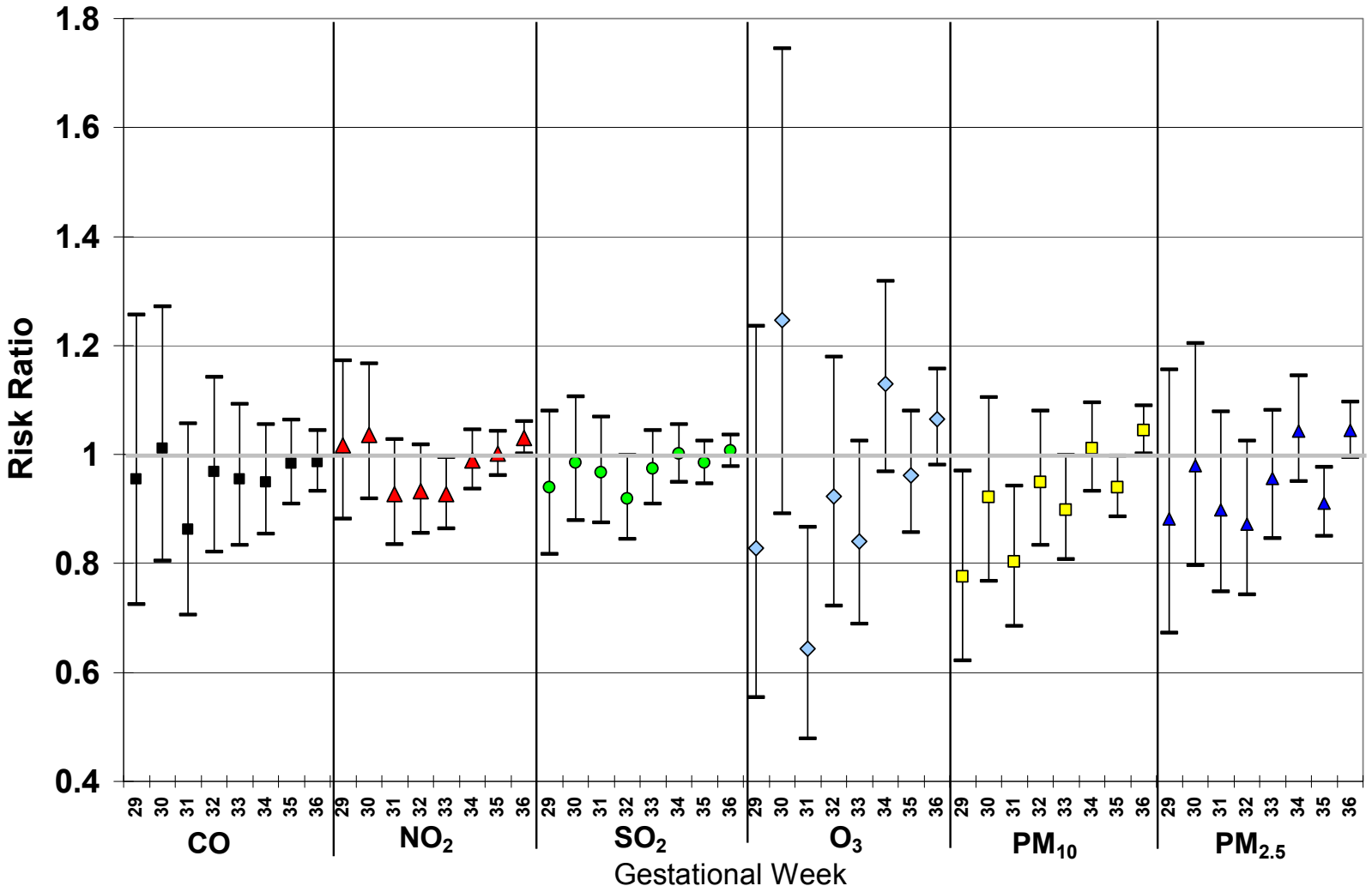


Table B11. Risk ratios, 95% confidence intervals* and p-values for ambient levels of air pollution and preterm birth for births to mothers residing inside the 285 perimeter highway (N births=121,000) using the population-weighted spatial average pollution from the five-county analysis

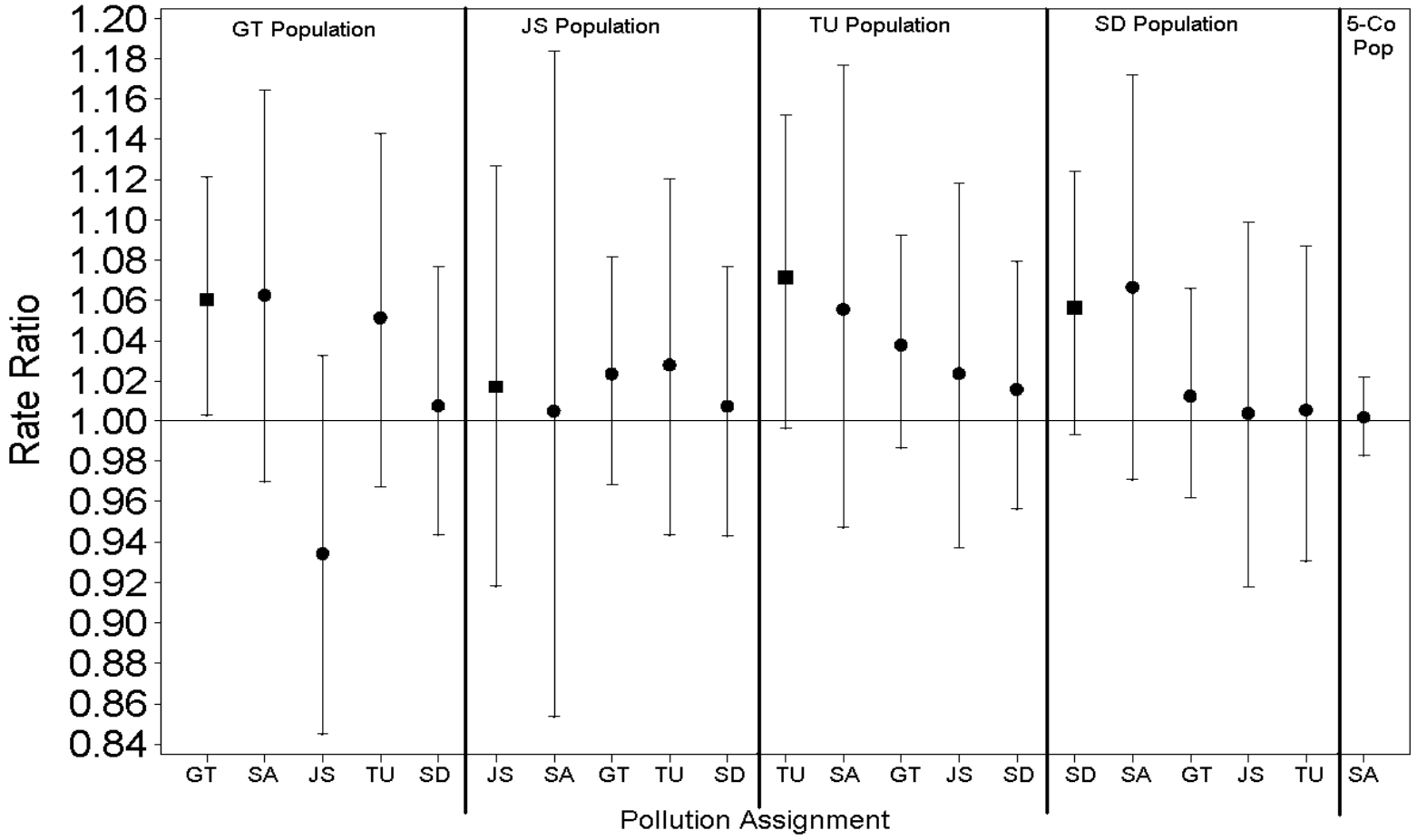
	First month of gestation¥		Final 1 week of pregnancy‡		Final 6 weeks of pregnancy‡	
Pollutant	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**	**RR (95% CI)**	**p**
1-hour max CO (ppm)	1.0068 (0.9586-1.0573)	0.79	1.0416 (1.0090-1.0752)	0.01	0.9974 (0.9317-1.0678)	0.94
1-hour max NO2 (ppb)	0.9698 (0.9446-0.9957)	0.02	1.0221 (0.9951-1.0498)	0.11	0.9997 (0.9646-1.0361)	0.99
1-hour max SO2 (ppb)	0.9734 (0.9429-1.0049)	0.10	1.0147 (0.9879-1.0423)	0.29	1.0092 (0.9749-1.0448)	0.60
8-hour max O3 (ppb)	0.9192 (0.8525-0.9911)	0.03	1.0143 (0.9651-1.0660)	0.58	0.9788 (0.8847-1.0829)	0.68
24-hour PM10 (µg/m3)	0.9804 (0.9445-1.0177)	0.30	1.0127 (0.9817-1.0447)	0.43	0.9840 (0.9333-1.0375)	0.55
24-hour PM2.5 (µg/m3)	0.9983 (0.9535-1.0452)	0.94	1.0006 (0.9654-1.0371)	0.97	0.9836 (0.9236-1.0475)	0.61
24-hour PM2.5-10 (µg/m3)	0.9863 (0.9440-1.0306)	0.54	0.9965 (0.9618-1.0325)	0.85	0.9894 (0.9366-1.0452)	0.70
24-hour PM2.5 SO4 (µg/m3)	0.9910 (0.9299-1.0561)	0.78	1.0090 (0.9634-1.0568)	0.70	0.9339 (0.8463-1.0306)	0.17
24-hour PM2.5 NO3 (µg/m3)	0.9990 (0.9243-1.0797)	0.98	1.0312 (0.9807-1.0843)	0.23	1.0549 (0.9553-1.1650)	0.29
24-hour PM2.5 OC (µg/m3)	0.9718 (0.9347-1.0105)	0.15	0.9895 (0.9565-1.0237)	0.54	0.9726 (0.9244-1.0233)	0.28
24-hour PM2.5 EC (µg/m3)	0.9687 (0.9282-1.0109)	0.14	1.0102 (0.9785-1.0429)	0.53	0.9866 (0.9263-1.0508)	0.67
24-hour PM2.5 TC (µg/m3)	0.9715 (0.9354-1.0090)	0.13	0.9964 (0.9634-1.0306)	0.84	0.9732 (0.9202-1.0292)	0.34
24-hour PM2.5 WS metals (µg/m3)	0.9834 (0.9123-1.0601)	0.66	1.0320 (0.9809-1.0857)	0.22	0.9274 (0.8283-1.0384)	0.19

* Risk ratios and 95% confidence intervals correspond to an IQR increase in the air pollutant value for each exposure window reported in Table 5.2
† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.
¥ Counts aggregated by conception date, offsetting by total conceptions, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education
‡ Counts aggregated by birth date, offsetting by gestations at risk, Poisson models control for long term trends, seasonal trends, maternal race/ethnicity, marital status, education, gestational week and interaction between gestational week and maternal characteristics. Extremely preterm births <29 weeks are excluded.

A positive association between NO_2 in the final six weeks of pregnancy and preterm birth was observed in the capture area analyses, but not in the five-county analyses. In the following analysis, we investigated whether the positive results observed in the capture-area analyses were more likely to be due to an improvement in exposure assessment by using the closest monitor, or to a susceptible urban population living near the monitors. The populations within four miles of each monitor were assigned pollution levels from each of the *other* individual NO_2 monitoring stations as well as the population-weighted spatial average used in the five-county analysis. If the association observed is attributable to a susceptible population, we might expect to observe elevated associations when each population is assigned pollution levels from the *other* individual NO_2 monitors and the five-county spatial average, not just when assigning pollution levels from the closest monitor. If the association observed is due to better exposure assessment, we would expect to observe the strongest associations when each population is assigned NO_2 exposures from its corresponding nearest monitor.

As shown in Figure B5, matching each population to its corresponding nearest monitor generally yields stronger observed associations than assigning levels from the other individual NO_2 monitors. This result is more compatible with an improvement in exposure assessment than a susceptible subpopulation living near the monitors. However, the estimated rate ratios using the spatial average (SA) are very similar to the rate ratios from the closest monitor, but with wider confidence intervals (less variability in the spatial average relative to the individual NO_2 monitors reduced power). These elevated rate ratios using the spatial average are in contrast to the rate ratio observed in the full five-county population shown on the far right of the figure. This suggests that population susceptibility may also partially explain why an association between NO_2 and preterm birth was observed in the capture-area analysis but not the five-county analysis.

Figure B5. Risk ratios and 95% confidence intervals for each population and NO_2 monitor combination, estimates reflect a 5 ppb increase in NO_2 levels in the final six weeks of gestation. Squares (■) indicate analyses where the population is matched to its corresponding monitor, circles (●) represent analyses where the population is matched to the spatial average (SA) or other individual NO2 monitors (GT, JS, TU, SD).



APPENDIX C

Additional analyses of ambient air pollution and small for gestational age in Atlanta, 1994-2004: a time-series analysis

Table C1. Tenth percentiles of birth weight for gestational age (in grams) within strata of race, sex and parity

Gestational Week	White				African American				Hispanic			
	Female		Male		Female		Male		Female		Male	
	Primi*	Multi	Primi	Multi	Primi	Multi	Primi	Multi	Primi	Multi	Primi	Multi
20	283	322	335	283	283	307	255	290	227	300	200	283
21	482	365	397	340	283	312	312	369	425	300	255	388
22	425	482	454	397	397	340	367	397	283	425	325	330
23	440	397	454	510	440	397	482	482	318	404	426	595
24	343	454	567	510	454	539	510	510	567	539	567	550
25	567	510	595	652	539	595	567	595	624	510	624	615
26	482	603	567	567	567	620	567	624	549	595	624	830
27	680	794	621	713	581	652	765	737	680	794	737	700
28	765	822	737	794	660	765	794	850	737	652	879	850
29	652	709	751	1134	822	950	936	900	907	1162	992	879
30	992	1049	1106	1077	936	1077	992	1106	890	1021	1287	964
31	1304	1191	1077	1389	1162	1191	1077	1280	1262	1219	1077	1304
32	1389	1361	1446	1616	1219	1446	1389	1417	1446	1219	1470	1503
33	1503	1644	1673	1800	1503	1616	1531	1616	1361	1857	1616	1786
34	1843	1928	1956	2041	1673	1843	1786	1843	1871	2041	1984	2070
35	2070	2211	2183	2325	1928	2080	1984	2098	2041	2268	2155	2268
36	2296	2381	2381	2495	2155	2240	2240	2360	2240	2410	2300	2495
37	2495	2637	2608	2778	2381	2466	2438	2577	2466	2637	2580	2722
38	2693	2835	2807	2948	2551	2637	2637	2750	2665	2807	2750	2892
39	2863	2948	2950	3062	2690	2750	2778	2863	2790	2892	2863	2980
40	2948	3033	3062	3147	2778	2807	2835	2948	2863	2977	2948	3062
41	3005	3062	3118	3203	2835	2863	2945	2977	2940	3010	3060	3147
42	2977	3062	3118	3175	2807	2835	2948	2920	2920	3005	3033	3147
43	2977	3033	3118	3118	2807	2807	2820	2920	2863	3060	2835	3062
44	2920	2948	3090	3203	2708	2722	2863	2892	2892	2977	3100	3090

*Primi=primiparous Multi=multiparous

Table C2. Spearman correlation coefficients between four-week average pollutant concentrations in five-county Atlanta.

	CO	NO_2	SO_2	O_3	PM_{10}	$PM_{2.5}$	CP	SO_4	NO_3	TC	EC	OC	WSMET
N observations	3833	3807	3769	3833	2929	2038	1765	1638	1635	1995	1995	1995	1648
CO	1												
NO_2	0.29	1											
SO_2	0.42	0.37	1										
O_3	-0.29	-0.07	-0.35	1									
PM_{10}	0.12	0.06	-0.17	0.78	1								
$PM_{2.5}$	0.11	0.08	-0.10	0.69	0.91	1							
CP ($PM_{2.5-10}$)	0.26	0.22	-0.19	0.57	0.74	0.64	1						
SO_4 ($PM_{2.5}$ sulfate)	-0.26	-0.26	-0.33	0.84	0.84	0.86	0.50	1					
NO_3 ($PM_{2.5}$ nitrate)	0.58	0.62	0.62	-0.68	-0.47	-0.37	-0.32	-0.59	1				
TC ($PM_{2.5}$ total carbon)	0.68	0.68	0.29	-0.09	0.32	0.29	0.33	-0.03	0.31	1			
EC ($PM_{2.5}$ elemental carbon)	0.80	0.61	0.32	-0.09	0.32	0.34	0.35	0.08	0.29	0.85	1		
OC ($PM_{2.5}$ organic carbon)	0.56	0.65	0.25	-0.08	0.30	0.23	0.14	-0.08	0.29	0.97	0.70	1	
WSMET ($PM_{2.5}$ WS metals)	-0.17	-0.21	-0.29	0.64	0.75	0.70	0.52	0.80	-0.58	0.07	0.16	-0.00	1

Time period: gases 9/1/93-2/28/2004 (3833 days), PM_{10} 1/1/1996-2/28/2004 (2981 days), $PM_{2.5}$ and components 8/1/1998-2/28/2004 (2038 days)

Table C3. Spearman correlation coefficients between nine-week average pollutant concentrations in five-county Atlanta.

	CO	NO_2	SO_2	O_3	PM_{10}	$PM_{2.5}$	CP	SO_4	NO_3	TC	EC	OC	WSMET
N observations	3957	3957	3919	3957	3167	2223	1930	1776	1733	2222	2222	2222	1776
CO	1												
NO_2	0.29	1											
SO_2	0.53	0.35	1										
O_3	-0.36	-0.17	-0.49	1									
PM_{10}	0.05	-0.09	-0.29	0.82	1								
$PM_{2.5}$	0.04	-0.11	-0.19	0.68	0.89	1							
CP ($PM_{2.5-10}$)	0.28	0.23	-0.19	0.51	0.64	0.55	1						
SO_4 ($PM_{2.5}$ sulfate)	-0.42	-0.49	-0.42	0.82	0.83	0.86	0.33	1					
NO_3 ($PM_{2.5}$ nitrate)	0.72	0.71	0.61	-0.70	-0.56	-0.47	-0.20	-0.74	1				
TC ($PM_{2.5}$ total carbon)	0.72	0.66	0.34	-0.27	0.14	0.15	0.16	-0.23	0.42	1			
EC ($PM_{2.5}$ elemental carbon)	0.79	0.55	0.40	-0.20	0.23	0.31	0.32	0.02	0.28	0.83	1		
OC ($PM_{2.5}$ organic carbon)	0.60	0.63	0.27	-0.29	0.07	0.03	0.06	-0.33	0.42	0.96	0.66	1	
WSMET ($PM_{2.5}$ WS metals)	-0.36	-0.45	-0.36	0.58	0.75	0.72	0.33	0.83	-0.69	-0.13	0.08	-0.24	1

Time period: gases 1/1/1994-10/31/2004 (3957 days), PM_{10} 3/1/1996-10/31/2004 (3167 days), $PM_{2.5}$ and components 10/1/1998-10/31/2004 (2223 days)

Table C4. Monitor-specific risk ratios and 95% confidence intervals* for ambient air pollution levels during selected gestational windows and preterm SGA for births within four miles of the station†

Pollutant Monitor	Dates of Operation	First month of gestation		Final 9 weeks of gestation	
		RR (95% CI)	pvalue	RR (95% CI)	pvalue
CO DeKalb Tech	9/93- 6/03	1.15 (1.01, 1.30)	0.04	0.82 (0.66, 1.02)	0.08
CO Roswell Rd.	8/94-12/04	1.09 (0.85, 1.40)	0.51	1.03 (0.70, 1.51)	0.88
CO Jefferson St.	8/98-12/04	1.08 (0.91, 1.28)	0.36	0.98 (0.76, 1.27)	0.89
NO_2 Georgia Tech	9/93-12/04	1.13 (0.97, 1.30)	0.11	1.11 (0.89, 1.38)	0.35
NO_2 Jefferson St.	8/98-12/04	0.90 (0.70, 1.16)	0.41	1.12 (0.79, 1.59)	0.51
NO_2 Tucker	4/95-12/04	1.08 (0.91, 1.28)	0.38	0.95 (0.71, 1.27)	0.72
NO_2 South DeKalb	9/93-12/04	1.01 (0.87, 1.17)	0.90	1.08 (0.88, 1.34)	0.45
O_3 Confederate Ave.	9/93-12/04‡	1.08 (0.64, 1.83)	0.76	0.53 (0.24, 1.17)	0.12
O_3 South DeKalb	9/93-12/04‡	1.46 (0.74, 2.91)	0.28	0.90 (0.30, 2.64)	0.84
O_3 Jefferson St.	8/98-12/04	1.06 (0.46, 2.47)	0.89	5.56 (1.68, 18.39)	0.01
SO_2 Confederate Ave.	9/93-12/04	1.12 (0.96, 1.32)	0.15	0.95 (0.79, 1.14)	0.58
SO_2 Jefferson St.	8/98-12/04	0.99 (0.80, 1.23)	0.92	0.85 (0.69, 1.04)	0.11
SO_2 Georgia Tech	9/93-12/04	1.06 (0.86, 1.31)	0.56	0.94 (0.74, 1.18)	0.58
PM_{10} Jefferson St.	8/98-12/04	1.39 (0.63, 3.06)	0.42	1.18 (0.40, 3.47)	0.76
PM_{10} Georgia Tech	1/96-12/04	1.25 (0.91, 1.72)	0.17	1.10 (0.68, 1.79)	0.68
$PM_{2.5}$ Jefferson St.	8/98-12/04	1.35 (0.94, 1.92)	0.10	1.21 (0.77, 1.92)	0.41
$PM_{2.5}$ Doraville Heath Center	3/99-12/04	1.16 (0.66, 2.03)	0.61	0.74 (0.32, 1.70)	0.47
$PM_{2.5}$ South DeKalb	3/99-12/04	1.15 (0.71, 1.85)	0.57	0.77 (0.18, 3.29)	0.73
$PM_{2.5}$ Tucker	3/99-12/04	0.79 (0.49, 1.28)	0.34	1.07 (0.57, 2.01)	0.83
$PM_{2.5}$ East Rivers School	3/99-12/04	0.76 (0.35, 1.67)	0.50	1.70 (0.29, 10.09)	0.56
$PM_{2.5}$ Fort McPherson	3/99-12/04	1.37 (0.79, 2.36)	0.26	1.26 (0.50, 3.16)	0.63
$PM_{2.5-10}$ Jefferson St.	8/98-12/04	1.34 (1.01, 1.78)	0.04	1.35 (0.96, 1.89)	0.08
$PM_{2.5}$ SO_4 Jefferson St.	8/98-12/04	1.33 (0.86, 2.05)	0.20	0.78 (0.38, 1.60)	0.49
$PM_{2.5}$ NO_3 Jefferson St.	8/98-12/04	1.02 (0.61, 1.69)	0.95	0.84 (0.42, 1.67)	0.62
$PM_{2.5}$ TC Jefferson St.	8/98-12/04	1.10 (0.86, 1.41)	0.46	1.58 (1.04, 2.39)	0.03
$PM_{2.5}$ EC Jefferson St.	8/98-12/04	1.09 (0.86, 1.39)	0.47	1.61 (1.05, 2.47)	0.03
$PM_{2.5}$ OC Jefferson St.	8/98-12/04	1.09 (0.85, 1.41)	0.49	1.41 (1.00, 1.98)	0.05
$PM_{2.5}$ WS metals Jefferson St.	8/98-12/04	1.17 0.71, 1.93)	0.53	0.71 (0.32, 1.61)	0.42

* Risk ratio and 95% CI's corresponds to a window-specific IQR increase in pollutant levels (shown in Table 6.2).

† Pooled inverse-variance weighted risk ratios for each pollutant and exposure window presented in Table 4. ‡ Did not operate in winter months

Table C5. Monitor-specific risk ratios and 95% confidence intervals* for ambient air pollution levels during selected gestational windows and full term SGA for births within four miles of the station†

Pollutant Monitor	Dates of Operation	First month of gestation		Weeks 28-36 of gestation		Final 9 weeks of gestation	
		RR (95% CI)	pvalue	RR (95% CI)	pvalue	RR (95% CI)	pvalue
CO DeKalb Tech	9/93- 6/03	1.04 (0.99, 1.09)	0.09	1.02 (0.94, 1.10)	0.69	1.02 (0.94, 1.10)	0.63
CO Roswell Rd.	8/94-12/04	1.02 (0.95, 1.10)	0.50	0.95 (0.85, 1.06)	0.36	0.95 (0.85, 1.06)	0.35
CO Jefferson St.	8/98-12/04	0.97 (0.92, 1.03)	0.29	1.04 (0.95, 1.13)	0.40	1.02 (0.94, 1.12)	0.59
NO_2 Georgia Tech	9/93-12/04	0.98 (0.94, 1.03)	0.46	0.94 (0.88, 1.01)	0.08	0.91 (0.85, 0.97)	0.01
NO_2 Jefferson St.	8/98-12/04	0.98 (0.90, 1.07)	0.60	1.08 (0.96, 1.21)	0.21	1.07 (0.96, 1.20)	0.24
NO_2 Tucker	4/95-12/04	1.05 (0.99, 1.11)	0.13	1.12 (1.01, 1.23)	0.03	1.08 (0.97, 1.19)	0.15
NO_2 South DeKalb	9/93-12/04	0.99 (0.94, 1.05)	0.72	0.99 (0.91, 1.07)	0.81	0.97 (0.89, 1.05)	0.42
O_3 Confederate Ave.	9/93-12/04‡	1.01 (0.85, 1.21)	0.87	0.98 (0.76, 1.26)	0.86	0.94 (0.73, 1.22)	0.65
O_3 South DeKalb	9/93-12/04‡	0.93 (0.72, 1.22)	0.61	1.10 (0.73, 1.66)	0.66	0.82 (0.54, 1.26)	0.37
O_3 Jefferson St.	8/98-12/04	0.86 (0.64, 1.14)	0.30	1.01 (0.69, 1.49)	0.94	0.96 (0.65, 1.40)	0.82
SO_2 Confederate Ave.	9/93-12/04	0.98 (0.92, 1.04)	0.49	0.99 (0.93, 1.05)	0.66	0.96 (0.90, 1.03)	0.25
SO_2 Jefferson St.	8/98-12/04	0.98 (0.91, 1.05)	0.60	1.02 (0.95, 1.09)	0.60	1.02 (0.95, 1.09)	0.60
SO_2 Georgia Tech	9/93-12/04	1.00 (0.94, 1.06)	0.97	0.97 (0.90, 1.05)	0.46	0.94 (0.87, 1.01)	0.08
PM_{10} Jefferson St.	8/98-12/04	0.85 (0.68, 1.08)	0.18	0.96 (0.69, 1.34)	0.81	0.96 (0.69, 1.33)	0.80
PM_{10} Georgia Tech	1/96-12/04	0.96 (0.87, 1.06)	0.41	0.89 (0.77, 1.03)	0.11	0.89 (0.77, 1.03)	0.13
$PM_{2.5}$ Jefferson St.	8/98-12/04	0.95 (0.83, 1.09)	0.48	1.02 (0.88, 1.19)	0.78	0.92 (0.79, 1.08)	0.31
$PM_{2.5}$ Doraville Heath Center	3/99-12/04	1.01 (0.86, 1.18)	0.89	1.11 (0.77, 1.60)	0.56	0.95 (0.66, 1.36)	0.79
$PM_{2.5}$ South DeKalb	3/99-12/04	1.02 (0.87, 1.20)	0.80	0.97 (0.53, 1.75)	0.91	0.83 (0.45, 1.53)	0.56
$PM_{2.5}$ Tucker	3/99-12/04	1.04 (0.87, 1.26)	0.65	1.09 (0.86, 1.38)	0.49	0.98 (0.76, 1.26)	0.88
$PM_{2.5}$ East Rivers School	3/99-12/04	1.07 (0.85, 1.34)	0.58	0.79 (0.47, 1.33)	0.38	1.56 (0.92, 2.65)	0.10
$PM_{2.5}$ Fort McPherson	3/99-12/04	1.13 (0.93, 1.39)	0.23	1.25 (0.93, 1.69)	0.13	1.13 (0.85, 1.51)	0.40
$PM_{2.5-10}$ Jefferson St.	8/98-12/04	1.01 (0.92, 1.11)	0.80	0.96 (0.86, 1.08)	0.54	0.96 (0.85, 1.07)	0.42
$PM_{2.5}$ SO_4 Jefferson St.	8/98-12/04	0.93 (0.81, 1.06)	0.28	0.99 (0.79, 1.25)	0.94	0.97 (0.77, 1.22)	0.80
$PM_{2.5}$ NO_3 Jefferson St.	8/98-12/04	0.95 (0.80, 1.12)	0.54	0.93 (0.75, 1.17)	0.55	0.87 (0.69, 1.09)	0.23
$PM_{2.5}$ TC Jefferson St.	8/98-12/04	0.99 (0.91, 1.07)	0.83	0.97 (0.85, 1.11)	0.68	1.03 (0.90, 1.19)	0.63
$PM_{2.5}$ EC Jefferson St.	8/98-12/04	0.98 (0.90, 1.06)	0.58	1.01 (0.88, 1.16)	0.88	1.04 (0.91, 1.20)	0.56
$PM_{2.5}$ OC Jefferson St.	8/98-12/04	1.00 (0.92, 1.08)	0.95	0.97 (0.86, 1.08)	0.53	1.02 (0.91, 1.14)	0.71
$PM_{2.5}$ WS metals Jefferson St.	8/98-12/04	0.92 (0.79, 1.08)	0.32	1.00 (0.76, 1.32)	0.97	1.07 (0.82, 1.40)	0.63

* Risk ratio and 95% CI's corresponds to a window-specific IQR increase in pollutant levels (shown in Table 6.2).
† Pooled inverse-variance weighted risk ratios for each pollutant and exposure window presented in Table 4. ‡ Did not operate in winter months

Table C6. Risk ratios and 95% confidence intervals for ambient air pollution levels in the nine weeks before birth and full term SGA for births in five-county Atlanta and for births within four miles of a monitor

	5 county ¥ RR (95% CI)	Near monitor Ψ RR (95% CI)
1-h max CO (ppm)	1.029 (0.985, 1.075)	1.005 (0.955, 1.057)
1-h max NO_2 (ppb)	1.007 (0.985, 1.030)	0.976 (0.935, 1.018)
1-h max SO_2 (ppb)	0.990 (0.970, 1.012)	0.973 (0.936, 1.013)
8-h max O_3 (ppb)	1.008 (0.949, 1.069)	0.920 (0.761, 1.114)
24-h PM_{10} ($\mu g/m^3$)	1.003 (0.973, 1.033)	0.904 (0.792, 1.032)
24-h $PM_{2.5}$ ($\mu g/m^3$)	1.006 (0.973, 1.039)	0.983 (0.881, 1.097)
24-h $PM_{2.5-10}$ ($\mu g/m^3$)	0.998 (0.968, 1.029)	0.955 (0.853, 1.069)
24-h $PM_{2.5}$ sulfate ($\mu g/m^3$)	0.983 (0.922, 1.048)	0.970 (0.771, 1.222)
24-h $PM_{2.5}$ nitrate ($\mu g/m^3$)	0.984 (0.927, 1.044)	0.871 (0.695, 1.092)
24-h $PM_{2.5}$ total carbon ($\mu g/m^3$)	1.003 (0.966, 1.041)	1.035 (0.901, 1.187)
24-h $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	1.002 (0.965, 1.041)	1.044 (0.906, 1.203)
24-h $PM_{2.5}$ organic carbon ($\mu g/m^3$)	1.002 (0.972, 1.033)	1.021 (0.913, 1.143)
24-h $PM_{2.5}$ water-soluble metals† ($\mu g/m^3$)	1.012 (0.939, 1.090)	1.069 (0.815, 1.402)

* $p<0.05$

** Risk ratios and 95% confidence intervals correspond to an IQR increase in pollutant value in the nine weeks before birth

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ SGA counts are limited to full term (≥37 weeks) aggregated by birth date, offset by total full term live births, Poisson models control for long term trends, seasonal trends, marital status, education

Table C7. Crude risk ratios and 95% confidence intervals for ambient air pollution levels in selected gestational windows and SGA for births in five-county Atlanta

	Full Term Births		Preterm Birth	
	First month of gestation ¥ RR (95% CI)	Weeks 28-36 of gestation Ψ RR (95% CI)	First month of gestation ¥ RR (95% CI)	Final 9 weeks of gestation ‡ RR (95% CI)
1-h max CO (ppm)	1.050 (1.036, 1.064)$	1.059 (1.045, 1.074)$	0.988 (0.953, 1.025)	0.983 (0.946, 1.023)
1-h max NO_2 (ppb)	0.994 (0.982, 1.006)	0.991 (0.976, 1.006)	0.993 (0.960, 1.028)	1.001 (0.960, 1.044)
1-h max SO_2 (ppb)	1.022 (1.009, 1.035)#	1.024 (1.012, 1.036)$	0.986 (0.952, 1.022)	0.995 (0.962, 1.028)
8-h max O_3 (ppb)	0.989 (0.973, 1.005)	1.003 (0.986, 1.020)	0.990 (0.946, 1.036)	0.981 (0.936, 1.029)
24-h PM_{10} ($\mu g/m^3$)	0.995 (0.982, 1.009)	1.018 (1.003, 1.033)*	0.987 (0.950, 1.026)	0.988 (0.948, 1.029)
24-h $PM_{2.5}$ ($\mu g/m^3$)	1.000 (0.984, 1.016)	1.019 (1.003, 1.034)*	0.976 (0.934, 1.020)	0.980 (0.939, 1.022)
24-h $PM_{2.5-10}$ ($\mu g/m^3$)	1.004 (0.989, 1.020)	1.010 (0.994, 1.027)	0.987 (0.947, 1.029)	0.986 (0.944, 1.039)
24-h $PM_{2.5}$ sulfate ($\mu g/m^3$)	1.000 (0.982, 1.018)	1.005 (0.983, 1.027)	0.986 (0.938, 1.037)	0.986 (0.930, 1.045)
24-h $PM_{2.5}$ nitrate ($\mu g/m^3$)	0.990 (0.969, 1.010)	1.003 (0.983, 1.023)	1.005 (0.949, 1.063)	1.028 (0.974, 1.085)
24-h $PM_{2.5}$ total carbon ($\mu g/m^3$)	1.022 (1.006, 1.039)#	1.032 (1.012, 1.053)#	1.029 (0.985, 1.075)	0.998 (0.944, 1.054)
24-h $PM_{2.5}$ elemental carbon ($\mu g/m^3$)	1.006 (0.994, 1.019)	1.028 (1.013, 1.043)#	1.003 (0.969, 1.038)	1.008 (0.967, 1.049)
24-h $PM_{2.5}$ organic carbon ($\mu g/m^3$)	1.030 (1.012, 1.048)#	1.022 (1.003, 1.041)*	1.044 (0.995, 1.095)	0.991 (0.942, 1.043)
24-h $PM_{2.5}$ water-soluble metals† ($\mu g/m^3$)	1.000 (0.981, 1.019)	1.008 (0.986, 1.030)	1.005 (0.952, 1.059)	0.967 (0.912, 1.027)

* $p<0.05$ # $p<0.01$ $ $p<0.0001$

** Risk ratios and 95% confidence intervals correspond to an IQR increase in pollution for each exposure window reported in Table 6.2

† Water-soluble metal index includes water soluble: Chromium, Copper, Iron, Manganese, Nickel, Vanadium.

¥ SGA counts aggregated by conception date, offset by total conceptions,

Ψ SGA counts aggregated at week 37 of gestation, offset by all gestations at 37 weeks gestation on given date

‡ SGA counts aggregated by birth date, offset by total live births

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