EXPOSURE TO PARTICULATE MATTER MASS AND SPECIES DURING PREGNANCY AND RISK OF BIRTH AT PRETERM GESTATIONAL AGES

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Abstract

KRISTEN MICHELLE RAPPAZZO: Exposure to particulate matter mass and species during pregnancy and risk of birth at preterm gestational ages
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Particulate matter <2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) has been variably associated with preterm birth (PTB), but the roles of $PM_{2.5}$ species have been less studied. In this work we examine associations between $PM_{2.5}$ mass and four $PM_{2.5}$ species and PTB. We estimated risk of birth in 4 preterm categories (risks reported as PTBs per 10^6 pregnancies) associated with change in ambient concentrations of $PM_{2.5}$ mass, elemental carbon (EC), organic carbons (OC), nitrates (NO_3), and sulfates (SO_4). From live birth certificates, we constructed a cohort of singleton pregnancies reaching 20 weeks of gestation between 2000-2005 (n=1,940,213; 8% PTB). We estimated mean exposures for each week of gestation from monitor-corrected Community Multi-Scale Air Quality modeling data. Risk differences (RD (95% confidence intervals)) for PTB categories (defined by gestational ages 20-27, 28-31, 32-34, and 35-36) were estimated for each exposure using modified Poisson linear regression, adjusted for maternal race, marital status, education, age, and ozone. RD estimates varied by exposure window, outcome period, and pollutant. Exposure to $PM_{2.5}$ at week four of gestation resulted in generally elevated risks, though magnitude varied by PTB category (e.g., for a 1$\mu g/m^3$ increase RD=11.8 (-6, 29.2); RD=46 (23.2, 68.9); RD=61.1 (22.6, 99.7); and RD=28.5 (-39, 95.7) for birth at weeks 20-27, 28-31, 32-34, and 35-36 respectively). Exposures

anchored at time of birth were associated with positive RDs for lags of 0-2 weeks across PTB categories. EC was associated with increased risks for births between 28-34 weeks (e.g., for a 0.25μg/m^3 increase in EC at gestational week 5, RD=84 (-5, 172) and RD=97 (-50, 243) for birth at weeks 28-31 and 32-34, respectively). Associations with OCs were generally null or negative. RDs for NO_3 were elevated in the early weeks of gestation and null in later weeks. RDs for SO_4 exposure were generally positively associated with PTB. EC and SO_4 appear to be influential contributors to $PM_{2.5}$'s role in PTB. Risk of PTB has diverse windows of vulnerability for exposure to species of $PM_{2.5}$. Because particulate matter exposure is ubiquitous, observation indicating harm is important for influencing regulatory standards.

This dissertation is dedicated to my parents, Charles J Rappazzo Jr. and Sheila A Rappazzo.

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List of Abbreviations

BC	British Columbia
BEIS3.12	Biogenic Emissions Inventory System
CA	California
CMAQ	Community Multi-scale Air Quality modeling system
CRP	C-reactive protein
CSN	Chemical Speciation Network
DAG	Directed acyclic graph
DNA	Deoxyribonucleic acid
DPV	Delivery Point Validation
EC	Elemental carbon
EMM	Effect measure modification
EPOS	Environment and Pregnancy Outcomes Study
ExPTB	Extremely preterm birth
FRM	Federal reference method
GA	Georgia
GIS	Geographic Information System
IDW	Inverse distance weighting
IMPROVE	Interagency Monitoring of Protected Visual Environments
IQR	Interquartile range
KZ	Kolmogorov–Zurbenko
LA	Los Angeles
LACS	Locatable Address Conversion System database

LPTB	Late preterm birth
LUR	Land use regression
MM5	National Center for Atmospheric Research/Penn State Mesoscale Model
MPTB	Moderate preterm birth
NH_4	Ammonium
NJ	New Jersey
NNH	Number needed to harm
NO_3	Nitrate
NOx	Nitrogen oxides
O_3	Ozone
OC	Organic carbons
OH	Ohio
OR	Odds Ratio
$PM_{0.1}$	Particulate matter under 0.1 micrometers in aerodynamic diameter
PM_{10}	Particulate matter under 10 micrometers in aerodynamic diameter
$PM_{2.5}$	Particulate matter under 2.5 micrometers in aerodynamic diameter
PA	Pennsylvania
PTB	Preterm birth
RD	Risk difference
ROS	Reactive oxygen species
SD	Standard deviation
SES	Socio-economic status
SLAMS	State and local air monitoring network

SMOKE	Sparse Matrix Operator Kernel Emissions
SO2	Sulfur dioxide
SO_4	Sulfate
STN	Speciation Trends Network
TIGER	Topologically Integrated Geographic Encoding and Referencing system
U.S. EPA	United States Environmental Protection Agency
VPTB	Very preterm birth
WHO	World Health Organization

Chapter 1: Specific Aims

Particulate matter under 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$), one of the criteria air pollutants regulated under the Clean Air Act, is a complex mixture of extremely small particles and liquid droplets. While levels of $PM_{2.5}$ vary across the United States, and are often below the United States Environmental Protection Agency (EPA) standards, $PM_{2.5}$ is a ubiquitous pollutant and everyone is exposed to some extent. $PM_{2.5}$ has been associated with a number of adverse health outcomes, including cardiovascular mortality, asthma, and poor pregnancy outcomes.(Backes et al. 2013; Dominici et al. 2003a; Dominici et al. 2006; Lewtas 2007; U.S.EPA. 2009) Of the pregnancy outcomes studied in conjunction with PM exposure, preterm birth is important because it is not only a marker for fetal underdevelopment, but also a risk factor for poor outcomes in later life, including but not limited to: infant mortality, acute respiratory and immunologic problems, cognitive deficits, and social-emotional problems.(Behrman 2006; Martin et al. 2007) Several studies have associated preterm birth with particulate matter of different size fractions from total suspended particles to coarse (PM_{10}) and fine particulate matter ($PM_{2.5}$).(Bobak 2000; Brauer et al. 2008; Darrow et al. 2009; Hansen et al. 2006; Huynh et al. 2006; Kim et al. 2007; Ritz et al. 2000; Ritz et al. 2007; Sagiv et al. 2005; Suh et al. 2008; Suh et al. 2009; Wilhelm and Ritz 2003; Xu et al. 1995; Yi et al. 2009) Variation in the magnitude of health effect associations between PM and adverse health outcomes, both spatially and temporally, suggest that the chemical components of particulate matter play a role in its toxicity, as these also vary spatially and

temporally.(Dominici et al. 2006; Dutton et al. 2009; Lippmann 2009; Schlesinger et al. 2006) However, the specific associations between these chemical components (e.g., elemental carbon, sulfate, etc) and health outcomes, including birth outcomes, are relatively understudied, leaving accountability for health effects unknown.(Lippmann 2009)

Studies of PM mass most frequently employ data from monitoring networks or land-use regression models for exposure assessment. These methods restrict either the population to within a certain distance of active monitors or the study area to a location with a relatively dense monitoring network (usually a large city). In addition, windows of exposure under study are frequently large (e.g., trimesters, entire pregnancy) making identification of specific periods of vulnerability to air pollution difficult to identify. Previous studies have also focused on any birth between 20-36 weeks as their outcome, when there may be shifts in etiology of preterm birth and vulnerability to $PM_{2.5}$ exposure based on gestational age.

Our purpose in this study was to examine the associations between $PM_{2.5}$ mass and $PM_{2.5}$ species for weekly windows of exposure and the risk of preterm birth at four categories of gestational age using an exposure assessment method that offers complete spatial and temporal coverage for our study area and period. Details of the analytic strategy taken to address these research questions can be found in chapter 3. Results of the analyses and conclusions are presented in manuscripts #1 entitled "Exposure to particulate matter during pregnancy and risk of birth at preterm gestational ages" (chapter 4) and #2 entitled "Exposure to elemental carbon, organic carbons, NO_3, and SO_4 during pregnancy and risk of birth at preterm gestational ages" (chapter 5). Chapter 6 closes

with my final observations of how this body of work contributes to the broader literature on this topic.

Specific Aim 1. Is increased exposure to fine particulate matter mass associated with increased risk of preterm birth?

- Objectives:
    1. To estimate risk differences for a 1 $\mu g/m^3$ increase in average exposure to $PM_{2.5}$ mass at each week of gestation for each of four categories of preterm birth.
    2. To estimate risk differences for a 1 $\mu g/m^3$ increase in average exposure to $PM_{2.5}$ mass for 1-week windows up to eight weeks lagged from birth for each of four categories of preterm birth.

Specific Aim 2. Is increased exposure to fine particulate matter species (sulfates, nitrates, organic carbons, and elemental carbon) associated with an increased risk of preterm birth?

- Objectives:
    1. To estimate risk differences for a 0.25 $\mu g/m^3$ increase in average exposure to elemental carbon at each week of gestation and for 1-week windows up to eight weeks lagged from birth for each of four categories of preterm birth.

2. To estimate risk differences for a 1 $\mu g/m^3$ increase in average exposure to organic carbons at each week of gestation and for 1-week windows up to eight weeks lagged from birth for each of four categories of preterm birth.
3. To estimate risk differences for a 1 $\mu g/m^3$ increase in average exposure to NO_3 nitrates at each week of gestation and for 1-week windows up to eight weeks lagged from birth for each of four categories of preterm birth.
4. To estimate risk differences for a 1 $\mu g/m^3$ increase in average exposure to SO_4 sulfates at each week of gestation and for 1-week windows up to eight weeks lagged from birth for each of four categories of preterm birth.

Chapter 2: Background and significance

Particulate matter under 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) is a ubiquitous air pollutant with known adverse health effects. One of the health effects $PM_{2.5}$ has been linked to is preterm birth, a marker of fetal underdevelopment and a risk factor for later poor health outcomes. It is likely that inflammatory processes underlie the link between $PM_{2.5}$ and preterm birth. Though the mechanism is not well understood at present, disruption of placental implantation and nutrient flow to the fetus have been put forth as pathways contributing to preterm delivery.

Several previous studies have linked exposure to $PM_{2.5}$ during pregnancy to preterm birth. Associations have been reported for exposures during early, middle, late, and entire pregnancy. The literature varies, in that disparate populations, study areas, study designs, exposure assessments, exposure metrics, et cetera are used to investigate the association. Many of the previous studies have employed monitor-based $PM_{2.5}$ assessments. Reliance on monitor activity patterns limits study populations both spatially and temporally. Studies also examined different exposure windows often of long duration, making it difficult to discern specific patterns of activity that might offer insight into mechanisms of $PM_{2.5}$'s actions on preterm birth.

Several studies have examined $PM_{2.5}$'s association with preterm birth, few have examined any of $PM_{2.5}$'s numerous species. This is likely due to lack of exposure information on the species, as such monitors are sparse. However, variation in $PM_{2.5}$ composition may explain variability in reported magnitudes of association with preterm

birth because one or more species comprising $PM_{2.5}$ may be driving the adverse health effects observed. Examining the associations between $PM_{2.5}$ mass and species and preterm birth provides better information for regulatory policies regarding this ubiquitous exposure and may identify subgroups potentially more vulnerable to the harmful effects from exposure.

2.1 Exposure - $PM_{2.5}$ and species

$PM_{2.5}$, one of the criteria air pollutants regulated under the Clean Air Act, is a complex mixture of extremely small particles and liquid droplets. $PM_{2.5}$ is a ubiquitous pollutant formed directly through emissions from sources such as electricity generating units, vehicle exhaust, fossil fuel combustion, and industrial processes. $PM_{2.5}$ may also be formed indirectly though atmospheric chemical reactions, such as the oxidation of hydrocarbons, sulfur dioxide (SO_2) gases, or nitrogen oxide (NO_x) gases.(U.S.EPA. 2009) In our study area, the highest $PM_{2.5}$ emitters are electricity generating units in Pennsylvania (PA) and Ohio (OH) and residential wood combustion in New Jersey (NJ) (Figure 1).(U.S.EPA.) The source profiles of PA and OH are similar, and while the source profile for NJ is different, it is likely that pollution from OH and especially PA are contributors to regional variation in NJ $PM_{2.5}$ concentrations.

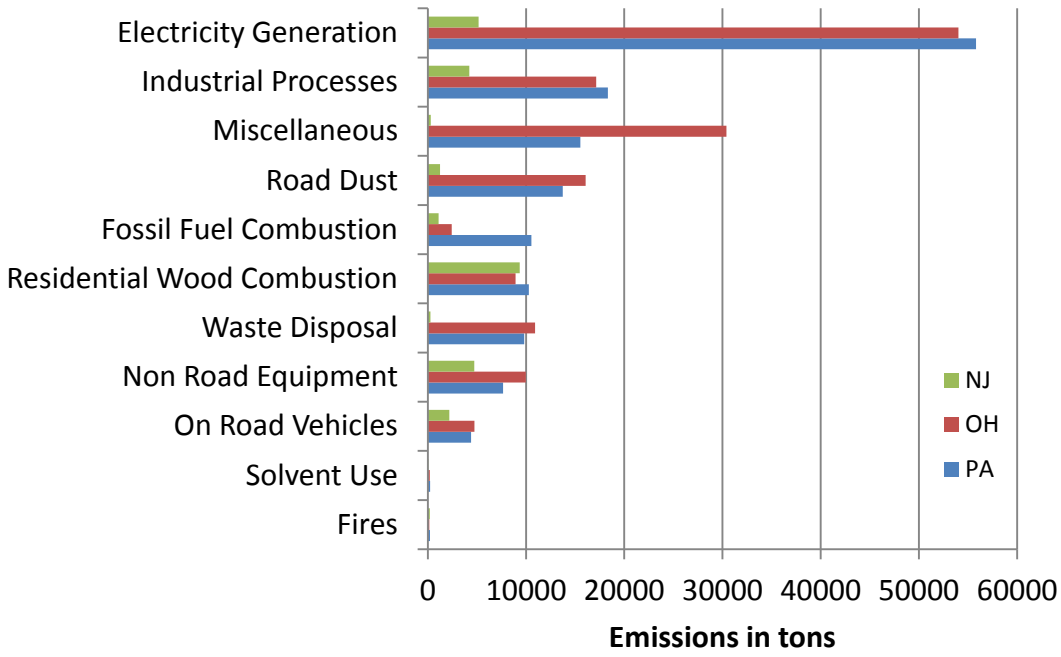


Figure 2.1: Fine particulate matter emission source profiles of New Jersey, Ohio, and Pennsylvania in 2005.(U.S.EPA.)

2.1.1 Composition of $PM_{2.5}$

The specific make-up of $PM_{2.5}$ varies on a number of scales both in time and space; regional, urban or local, daily, weekly, and seasonal changes are all present based on local and regional sources of pollution and factors such as temperature and weather conditions.(U.S.EPA. 2009) Our study focuses on four components or species that make up a large proportion of $PM_{2.5}$: elemental carbon (EC), organic carbons (OC), sulfate (SO_4), and nitrate (NO_3). These components were identified in a study of spatial and temporal variability of $PM_{2.5}$ as each contributing greater than 1% to $PM_{2.5}$ mass.(Bell et al. 2007) Sulfate is much elevated in the eastern and northeastern US, particularly in the summer months, where it accounts for a fifth to a half of $PM_{2.5}$ mass.(Bell et al. 2007; NARSTO 2004) Nitrate concentrations by contrast are elevated in the winter across the US.(Bell et al. 2007; NARSTO 2004) Nitrate precursors nitric acid and ammonia are

likely to be higher in urban areas, where nitrate itself is also elevated.(NARSTO 2004) Organic carbon contributes to a large proportion of $PM_{2.5}$ mass across the US during all seasons, though is highest in the summer months.(Bell et al. 2007; NARSTO 2004) Elemental carbon accounts for a lower percentage of total $PM_{2.5}$ mass than the other species but shows both regional and seasonal variation in concentrations.(Bell et al. 2007)

2.1.2 Measurement

$PM_{2.5}$ is measured through monitoring networks employing the federal reference method (FRM) which was implemented in response to its addition in 1997 to the Clean Air Act. The State and Local Air Monitoring Stations network (SLAMS) consists of approximately 1500 $PM_{2.5}$ monitoring sites across the United States, including 150 sites where $PM_{2.5}$ speciation occurs.(USEPA 2006a, b) In addition, the Speciation Trends Network (STN), established in 1999 to provide nationally consistent speciated $PM_{2.5}$ data for urban areas across the county, contributes 54 sites to $PM_{2.5}$ species monitoring.(Rao et al. 2003) Air monitors undergo regular quality control testing and are frequently used in large scale air pollution studies. Testing of air monitors has generally demonstrated excellent precision (less than 5% difference) and accuracy (within 10%).(U.S.EPA. 2009) $PM_{2.5}$ monitors typically take measurements every three or six days, rather than daily or hourly. As data from monitors are limited spatially and temporally, the use of models to estimate air pollution concentrations has become more popular. One of these modeling methods is the Community Multiscale Air Quality (CMAQ) model, which incorporates pollutant emissions and meteorological conditions then simulates chemical and physical processes and chemical transport occurring in the atmosphere to estimate gridded

concentrations of ambient air pollutants, including $PM_{2.5}$.(Byun and Schere 2006; Hogrefe et al. 2009) With the CMAQ model, air pollutant concentrations can be simulated for each day and over a wide area.(Marmur et al. 2004) While PM monitoring data is available only every 3 or 6 days and at monitoring locations, CMAQ estimates are available daily across the United States, including rural and other unmonitored areas. There may be some sacrifice of spatial resolution, as CMAQ estimates are currently generated for $12km^2$ grids, but in areas with few monitors this grid may offer higher resolution.

2.1.3 Health effects of $PM_{2.5}$

Particulate matter is one of the criteria air pollutants with both known and probable adverse health effects. There is a large body of literature linking mortality and cardiovascular outcomes (e.g., coronary heart disease, stroke, cardiovascular mortality) to short and long term exposures to $PM_{2.5}$.(Dominici et al. 2003a, b; Dominici et al. 2006; Lewtas 2007; Sun et al. 2010) Many studies have also examined the effects of PM on the respiratory system, and found links to bronchitis, pneumonia, pulmonary function, asthma, and allergy response.(U.S.EPA. 2009) In both epidemiologic and toxicologic literature PM is associated with lung cancer, and mortality due to lung cancer and has evidenced some mutagenic and genotoxic properties.(U.S.EPA. 2009) There are also a number of reproductive outcomes linked to particulate matter exposure.(Backes et al. 2013; Stieb et al. 2012)

The strength of associations between PM and health effects vary spatially and temporally, as does the chemical composition and make-up of PM.(Bell et al. 2007;

Dutton et al. 2009; Lippmann 2009) The variation in both strength of associations and chemical composition likely indicates a role for $PM_{2.5}$ speciates and differing toxicity with alternate compositions.(Schlesinger et al. 2006) The health effects of chemical components of $PM_{2.5}$ have been examined by comparatively few studies, likely due to limited data resources for $PM_{2.5}$ speciation. Various $PM_{2.5}$ species (e.g., elemental carbon, metals, sodium ions, organic carbons, sulfate, and nitrate) have been associated with health effects including higher risk of hospitalizations, mortality, and preterm birth.(Atkinson et al. 2010; Bell et al. 2007; Darrow et al. 2009; Franklin et al. 2008; Gehring et al. 2011; Peng et al. 2009; Wilhelm et al. 2011; Zanobetti et al. 2009)

2.2 Preterm birth

Preterm birth (PTB) is defined by the WHO as live births occurring before 37 completed weeks of gestation.(WHO 1992) While gestational age has no bearing on the definition of live birth, the lower limit of viability is usually around 20 weeks of completed gestation. Births at less than 32 and 28 weeks completed gestation are considered very preterm and extremely preterm, respectively.(Behrman and Butler 2007) In 2005, 11% of singleton births in the United States were considered preterm, with 16.5% of singleton births to non-Hispanic black women and 9.7% of singleton births to non-Hispanic white women being preterm, though non-Hispanic black women account for less than 15% of all births.(Martin et al. 2007; Mathews and MacDorman 2010)

2.2.1 Health effects of preterm birth

Preterm birth is both a marker for underdevelopment of fetal systems and a risk factor for further adverse health outcomes. Preterm birth is one of the strongest predictors of early infant mortality; approximately two-thirds of infants who die were born preterm, and of these one third are attributable to complications of preterm birth.(Behrman and Butler 2007; Callaghan et al. 2006; Mathews and MacDorman 2010) Compared to term infants, preterm infants are at increased risk of many acute (i.e., neonatal period) complications (e.g., respiratory distress and bronchopulmonary dysplasia, necrotizing enterocolitis, infections, rehospitalizations, etc.).(Behrman and Butler 2007; Mathews and MacDorman 2010; Saigal and Doyle 2008) Preterm birth is associated with a spectrum of neurodevelopmental issues, poorer growth, and lower general health. From cerebral palsy, intellectual disability, and visual and hearing impairments to learning disabilities, attention problems, hyperactivity, poor coordination, and socio-emotional problems.(Behrman and Butler 2007) In addition to the health consequences of preterm birth, there are also economic consequences beginning with immediate medical care services and followed by educational services, lost productivity, secondary costs associated with hospital stays (travel, child care), and longer term undocumented costs to individuals, families and society.(Behrman and Butler 2007; Petrou et al. 2001)

2.3 Potential mechanisms

Particulate matter may adversely impact health through physical characteristics such as size, surface, morphology, mass concentration, numbers of particles, or electrical properties.(Reiss et al. 2007) $PM_{2.5}$ may also act through physical chemistry:

hygroscopicity, hydrophilicity, lipophilicity, bioavailability, acidity, redox potential, and surface chemistry.(Reiss et al. 2007) Finally, $PM_{2.5}$ may act through chemical properties and species: metals, EC, OC, sulfate, nitrate, etc.(Reiss et al. 2007) Differences in the chemical composition of $PM_{2.5}$ may account for some of the geographic and temporal differences in direction and magnitude of associations between $PM_{2.5}$ and health outcomes, particularly as the toxicity of each species varies.(Schlesinger et al. 2006)

The mechanisms of $PM_{2.5}$'s actions on preterm birth are not well understood at present. The potential pathways include inflammation, oxidative stress, and infection or infection susceptibility. In terms of inflammation, particles may act at the lung or respiratory interface (pulmonary inflammation triggering systemic inflammation) or soluble components may be absorbed/translocated into bloodstream and interact directly with cells/organ systems.(U.S.EPA. 2009) Inflammation may also be a consequence of reactive components (e.g., reactive oxygen species (ROS)) of $PM_{2.5}$.(U.S.EPA. 2009) In addition to inflammation, oxidative stress from ROSs may cause cell damage, DNA damage, disruption of cellular processes, irreversible protein modifications, or alternations in cellular signaling.(U.S.EPA. 2009) Inflammation may result in disruption of placental implantation or altered placental development or vascular function leading to impaired nutrient exchange between mother and fetus.(Kannan et al. 2006) $PM_{2.5}$ may influence infection, which in turn initiates inflammatory processes, by increasing susceptibility to infectious agents after exposure.(U.S.EPA. 2009) Infection has been associated with preterm birth and may initiate premature contractions or rupture of membranes.(Behrman and Butler 2007; Wilhelm and Ritz 2005) Infection may cause preterm labor, particularly preterm premature rupture of membranes, through increases in

production of pro-inflammatory cytokines, prostaglandins, or matrix metalloproteinases—which degrade collagens.(Behrman and Butler 2007) PM has also been linked to changes in hemodynamic responses (e.g., increases in blood pressure/hypertension), coagulation, and alteration of endothelial function.(Kannan et al. 2006; Ritz and Wilhelm 2008) Coagulation and endothelial function alteration may lead to vasoconstriction and nutritional deprivation, followed by the potential for preterm birth. Hypertension, which has been linked to intra-uterine growth restriction, may also lead to fetal malnutrition and therefore increase potential for initiation of preterm labor.(Kannan et al. 2006; Ritz and Wilhelm 2008) Activation of the fetal hypothalamic-pituitary-adrenal axis is a part of the preparation for normal labor.(Behrman and Butler 2007) There is some evidence in animal research that PM may influence the hypothalamic-pituitary-adrenal axis, and it is possible that exposure to PM may prematurely activate the fetal hypothalamic-pituitary-adrenal axis leading to preterm birth.(U.S.EPA. 2009; Zhao et al. 2011)

2.4 Epidemiology of $PM_{2.5}$ and preterm birth

Since 2005, there have been fifteen studies examining the associations between $PM_{2.5}$ and preterm birth (table 1). Four studies of $PM_{2.5}$ and preterm birth also examine the associations between at least one $PM_{2.5}$ species and preterm birth (table 2). Cohort study designs dominate, as do use of $PM_{2.5}$ monitors as source of exposure data, though more recent studies are using methods to expand exposure information beyond what monitors can provide (e.g., land-use regression models (LUR)). Exposure contrasts examined range between 1 to 10$\mu g/m^3$ $PM_{2.5}$ mass. Eleven of the study populations are

from the United States, with over half of those from California. These studies investigate differing study populations and research methodologies (e.g., exposure assessments, metrics, contrasts, and study designs), making direct comparisons and interpretation of disparate results across studies challenging.

2.4.1 Epidemiology of $PM_{2.5}$ and preterm birth

Studies examining entire pregnancy exposures to $PM_{2.5}$ have found positive odds ratios (OR), though exposure contrasts and magnitudes of effect vary by study.(Brauer et al. 2008; Chang et al. 2012; Gehring et al. 2011; Huynh et al. 2006; Kloog et al. 2012; Wilhelm et al. 2011; Wu et al. 2009; Wu et al. 2011) Four of these studies occurred in the Los Angeles CA area and found mostly consistent positive effects.(Huynh et al. 2006; Wilhelm et al. 2011; Wu et al. 2009; Wu et al. 2011) For $PM_{2.5}$ exposures in early pregnancy, five studies across different geographic areas have found positive odds ratios (OR).(Chang et al. 2012; Hansen et al. 2006; Huynh et al. 2006; Jalaludin et al. 2007; Lee et al. 2012; Ritz et al. 2007) Fewer studies have reported positive associations for exposures late in pregnancy or near birth, but among those that have, effects are generally consistent (ORs ~1.05).(Chang et al. 2012; Gehring et al. 2011; Hansen et al. 2006; Wilhelm and Ritz 2005) Effects of $PM_{2.5}$ exposures in middle pregnancy have been less reported; however Chang et al.(2012) found effects with exposure to $PM_{2.5}$ in both the first and second trimesters. These studies primarily used monitors or monitoring based methods (e.g., kriging, land-use regression) of exposure assessment. While kriging and land use regression provide improvement in exposures for some studies by imputing complete spatial and temporal coverage, those methods are best suited for areas with

reasonably dense spatial and temporal monitoring (e.g. larger cities). Chang et al.(2012) examined $PM_{2.5}$ exposure in North Carolina using both monitor data and monitor-corrected CMAQ data, finding similar results for women with exposure information from both sources. Warren et al.(2012) evaluated weekly windows of exposure, finding elevated risks with $PM_{2.5}$ exposure in weeks 4-22 of gestation.

A handful of studies have reported inverse or null ORs with $PM_{2.5}$ exposure in early pregnancy. Jalaludin et al.(2007) found inverse ORs, though only for exposures occurring in summer months. Gehring et al.(2011) found inverse associations with $PM_{2.5}$ exposures in the first trimester and last month before birth, though with adjustment for region these effects were attenuated (first trimester) or reversed (last month before birth). This shift in effect with regional adjustment may suggest the association varies depending on $PM_{2.5}$ composition. Darrow et al.(2009) found null risk ratios for exposures in the first month of gestation and one week before birth. Interestingly both studies using a more specific definition of preterm birth (27-36 weeks for Chang et al.(2012) and 29-36 weeks for Darrow et al.(2009)), reported opposing results for the first trimester/month of pregnancy exposure. However, this may be due to differences in study design, as Chang et al.(2012) examined PTB as a time-to-event analysis and Darrow et al.(2009) employed a time-series approach. In two studies, Wilhelm et al. found inverse ORs with single pollutant models of $PM_{2.5}$ for exposures in early pregnancy (Wilhelm and Ritz 2005; Wilhelm et al. 2011); however, in the later study, analysis using multi-pollutant models produced positive ORs for $PM_{2.5}$ exposure.(Wilhelm et al. 2011) This suggests that adjusting for co-occurring pollutants might bring about shifts from inverse or null to

positive effect estimates, addressing confounding of the PM2.5-PTB association by those co-pollutants.

2.4.2 Epidemiology of $PM_{2.5}$ species and preterm birth

$PM_{2.5}$ species and preterm birth has been less studied. Currently, only four studies are published on this topic, but vary in design, exposure, and exposure assessment methods. Two studies used LUR methods to examine the effects of soot or black carbon (a close but not complete corollary to elemental carbon). While Brauer et al.(2008) found no effect of black carbon with entire pregnancy exposures, Gehring et al.(2011) found positive ORs with entire pregnancy and last month exposures. Both of their LUR models had potential downfalls. Brauer et al's(2008) model performed poorly in evaluation tests and used $PM_{2.5}$ data for seasonal adjustment as black carbon data was unavailable. Gehring et al.(2011) constructed exposures using environmental data from 1999/2000 for pregnancies in 1996/97, assuming no change in spatial variation of soot/$PM_{2.5}$ between the two periods though lacking data to check this assumption.

Two studies examined a variety of $PM_{2.5}$ species. In a time-series study of the Atlanta area, Darrow et al.(2009) observed positive risk ratios for nitrates and sulfates with exposure in the 1st month of pregnancy and for sulfates and EC with a 1 week lag from birth; OCs had null effects for all exposure windows examined. Wilhelm et al.(2011) used a case-control design with entire pregnancy exposures and found elevated odds ratios with exposure to EC, OC, and ammonium nitrate in single pollutant models and ammonium nitrate in multi-pollutant models. Odds were null for ammonium sulfate in single-pollutant models and inverse in multi-pollutant models.

Table 2.1: Summary of epidemiologic studies of $PM_{2.5}$ and preterm birth

Author & year	Study period, location, & design	Subjects & recruitment	Exposure contrast	Exposure details	Results Windows of exposure Early (within 1st trimester)	Late (3rd trimester, weeks from birth)	Whole pregnancy
Wilhelm and Ritz, 2005	1994-2000	9,268 cases	10 µg/m3	Distance ≤ 1 mi	0.85 (0.70, 1.02)	1.09 (0.91, 1.30)	
	LA, CA, USA	106,483 controls		1 < d ≤ 2 mi	0.85 (0.74, 0.99)	1.08 (0.97, 1.21)	
	case-control	registry		2 < d ≤ 4 mi	0.83 (0.78, 0.88)	1.05 (0.99, 1.10)	
				ZIP-code	0.73 (0.67, 0.80)	1.10 (1.00, 1.21)	
Huynh et al, 2006	1999-2000	10673 cases	10 µg/m3		1.13 (1.12, 1.13)	1.06 (1.05, 1.06)	1.15 (1.15, 1.16)
	CA, USA	32019 controls					
	case-control	registry					
Brauer et. al., 2008	1999-2002	70,249 births	1µg/m3	LUR*			1.07 (0.98, 1.16)
	Vancouver, BC, Canada	registry		IDW**			1.13 (0.92, 1.39)
	Cohort						
Jalaludin et al, 2007	1998-2000	123,840 births	1µg/m3	fall	1.08 (0.91, 1.28)		
	Sydney, Australia	registry		winter	1.43 (1.26, 1.61)		
	Cohort			spring	1.16 (0.97, 1.38)		
				summer	0.88 (0.84, 0.92)		
Ritz et al, 2007	2003	58,316 births	<=18.63	full cohort	reference		
	LA, CA, USA	2,543 EPOS subset	18.64-21.36		1.01 (0.93, 1.09)		
	Cohort	registry	>21.36		1.10 (1.01, 1.2)		
			<=18.63	EPOS	reference		
			18.64-21.36		1.14 (0.90, 1.46)		
			>21.36		1.27 (0.99, 1.64)		
Hansen et al, 2006	2000-2003	28,200 births	10.0 Mm^-1		1.09 (0.97, 1.23)		
	Brisbane, Australia	registry	8.2 Mm^-1			1.09 (0.97, 1.23)	
	Cohort						
Wu et al, 2009	1997-2006	81,186 births	1.35	<37 weeks			1.03 (1.01, 1.06)

			µg/m3			
	LA, CA, USA	hospital registry		<35 weeks		1.07 (1.03, 1.12)
	Cohort			<30 weeks		1.18 (1.10, 1.26)
Gehring et. al., 2011	1996-1997	3863 births	4.5 µg/m3			1.22 (0.83, 1.80)
	The Netherlands	Prevention and Incidence of Asthma and Mite Allergy study	7.8 µg/m3	0.98 (0.75, 1.29)		
	Cohort		5.3 µg/m3		1.06 (0.84, 1.35)	
Darrow et al, 2009	1998-2004	293,688 births	5-6 µg/m3	0.99 (0.93, 1.05)		
	Atlanta, GA, USA	registry		1 week lag	1.00 (0.96, 1.03)	
	Time-series			6 week lag	1.05 (0.96, 1.16)	
Lee et al. 2012	1997-2002	34,705 women	4.0 µg/m^3	1.10 (1.01, 1.20)		
	Allegheny county, PA USA	MOMI database				
	cohort					
Wu et al. 2011	1998-2006	81,186 singleton births	5.1 µg/m3	monitor data, LA county		1.04 (0.94, 1.15)
	LA & Orange Counties, CA USA			monitor data, Orange County		1.09 (1.00, 1.20)
	cohort	birth records	1.4 µg/m3	CALINE model, LA county		1.04 (1.00, 1.08)
				CALINE model, Orange County		1.02 (0.97, 1.07)
Kloog et al. 2012	2000-2008	634,244 singleton births	10 µg/m3			1.06(1.01, 1.03)
	Massachusetts USA	birth records				
	cohort					
Wilhelm et al. 2011	6/1/2004 - 3/30/2006	10,265 preterm births	2.6 µg/m3	single-pollutant model		0.91(0.88, 0.94)
	LA County, CA	102,650 controls		multi-pollutant model		1.11(1.02, 1.20)

	case-control	birth records					
Chang et al. 2012	2001-2005	161,078 - 453,562 singleton births	1.73 µg/m3	cumulative			1.07 (1.01, 1.14)
	North Carolina USA	birth records		Trimester 1	1.02 (0.96, 1.08)		
	cohort			Trimester 3		1.03 (0.98, 1.08)	
				Weeks 1 -6	1.03 (0.98, 1.07)		
				6-week lag		1.01 (0.97, 1.06)	
				1-week lag		1.01 (0.98, 1.04)	
				Trimester 2		1.03 (0.95, 1.11)	
Warren et al. 2011	2002-2004	450,000 births			increases in preterm birth with exposures in weeks 4-22		
	Texas USA	birth records					
	cohort						

*Land use regression

**inverse distance weighing

Table 2.2: Epidemiologic studies of $PM_{2.5}$ species and preterm birth

Author & Year	Study period, location, & design	Subjects & recruitment	Exposure contrast	Exposure details	Results Windows of exposure Early (within 1st trimester)	Late (3rd trimester, weeks from birth)	Whole pregnancy
Gehring et. al., 2011	1996-1997 The Netherlands Cohort	3863 births Prevention and Incidence of Asthma and Mite Allergy study	soot 0.94 $x10^{-5}m^{-1}$ 2.46 $x10^{-5}m^{-1}$ 1.47 $x10^{-5}m^{-1}$		 0.94 (0.72, 1.23)	 1.12 (0.96, 1.32)	1.27 (0.96, 1.67)
Brauer et. al., 2008	1999-2002 Vancouver, BC, Canada Cohort	70,249 births registry	Black carbon 10^-5/m				0.99 (0.87–1.13)
Darrow et. al., 2009	1998-2004 Atlanta, GA, USA Time-series	293,688 births registry	Elemental carbon 0.53-0.70 µg/m3	 1 week lag 6 week lag	1.01 (0.93, 1.10)	 1.04 (0.98, 1.10) 0.97 (0.86, 1.08)	
			Organic carbon 1.2-1.7 µg/m3	 1 week lag 6 week lag	1.02 (0.94, 1.10)	 1.01 (0.95, 1.08) 0.98 (0.89, 1.07)	
			Total carbon 1.6 - 2.3 µg/m3	 1 week lag 6 week lag	1.02 (0.95–1.09)	 1.02 (0.96, 1.09) 0.97 (0.88, 1.08)	
			Nitrates 0.64 - 0.75 µg/m3	 1 week lag 6 week lag	1.03 (0.89, 1.20)	 0.98 (0.90, 1.08) 0.86 (0.71, 1.04)	
			Sulfates 2.8 - 3.0 µg/m3	 1 week lag 6 week lag	1.06 (0.94, 1.20)	 1.09 (1.01, 1.19) 0.93 (0.77, 1.11)	
			Water-soluble metals 0.016-0.020 µg/m3	 1 week lag 6 week lag	1.07 (0.93, 1.24)	 1.11(1.02, 1.22) 0.89 (0.72, 1.09)	

Wilhelm et al. 2011	6/1/2004 - 3/30/2006 LA county, CA USA case-control	10,265 preterm births 102,650 controls birth records	Elemental carbon 0.55 µg/m3	single-pollutant model	1.11 (1.07, 1.15)
			Organic carbons 1.3 µg/m3	single-pollutant model	1.05 (1.03, 1.06)
			Ammonium sulfate 1.8 µg/m3	single-pollutant model multi-pollutant models	1.00 (0.98, 1.02) ~ 0.89 (0.83, 0.95)
			Ammonium nitrate 1.8 µg/m3	single-pollutant model multi-pollutant models	1.11 (1.08, 1.14) ~ 1.40 (1.29, 1.52)

2.5 Limitations of current research

Exposure misclassification is the major limitation within the current literature of air pollution and birth outcomes. Individual level monitoring is unfeasible due to analysis expense and participant burden necessary for studies of birth outcomes; therefore researchers assign ecologic measures of exposure to study subjects. This leads to misclassification as individual experiences (e.g., time spent at the residence, time spent at other locations, indoor versus outdoor exposure, physical activity, etc) are not taken into account.(Bell 2006; Bobak and Leon 1999) In a study of French cities, Nerriere et al. found that ambient PM monitors underestimate individual exposures across a variety of circumstances.(Nerriere et al. 2005) However, studies in Baltimore, MD have found ambient measures of $PM_{2.5}$ to be fairly accurate proxies for individual exposure, and high correlation between indoor and outdoor $PM_{2.5}$.(Sarnat et al. 2000; Sarnat et al. 2005; Williams et al. 2000)

One method to achieve greater exposure accuracy is to restrict analysis to subjects living within a certain mile radius of an air monitor for a particular pollutant, usually 2 to 5 miles. This method has the benefit of giving reasonably accurate pollutant information,(Basu et al. 2004) but has the drawback of greatly restricting the subject pool the study may draw from. This may cause selection bias or reduce generalizability as women living near to monitoring sites may have different characteristics as women living farther from them.(Woodruff et al. 2009)

Most studies rely on ambient monitors for exposure data. Data from these monitors offer a number of advantages because they are convenient, widespread, and publicly available; but the representativeness of ambient data to an individual's exposures

is not known. Some studies of infant mortality have concluded that ambient PM monitors underestimate individual exposures across a variety of circumstances, while others have reported ambient measures of $PM_{2.5}$ to be fairly accurate proxies for individual exposure with high correlation between indoor and outdoor $PM_{2.5}$.(Ha et al. 2003; Hajat et al. 2007; Kaiser et al. 2004; Loomis et al. 1999) Monitoring sites are usually located in urban areas, leading to a lack of information for more rural locations. PM monitors offer temporal resolution of at best 3 days and may not be active throughout the year, leading to temporal data gaps and potential exclusion of women living near monitors during inactive periods. In recent years, land-use regression modeling, which characterizes air pollutant concentrations based on area variables such as traffic density and land cover, has been employed in some studies. However, LURs depend upon relatively dense monitoring networks, thus are often performed in large cities. While LURs improve spatial resolution and can fill in temporal gaps in monitored concentrations, issues of exclusion and generalizability remain.

There is a lack of $PM_{2.5}$ speciation data and studies examining associations with $PM_{2.5}$ species and preterm birth. The number of studies employing speciated $PM_{2.5}$ data has risen in recent years, however this data remains limited, and only four studies of preterm birth examined the association with $PM_{2.5}$ species. These studies were themselves limited by how concentrations and exposures were determined (e.g., use of monitors or non-validated models) or by only examining a single $PM_{2.5}$ species. Examining a single $PM_{2.5}$ species may not offer much advantage over studying $PM_{2.5}$ mass, as due to high correlation between species it is likely that some mass variation is captured when examining only a single species in a model. Similar models were used to estimate black

carbon concentrations in two studies. In both studies, data on black carbon was unavailable for certain time periods and had to be estimated using an alternate component of $PM_{2.5}$ or $PM_{2.5}$ mass, potentially leading to misclassified exposures. For one of the studies, subjects were born years before data on black carbon were available, and so exposure concentrations were back-calculated based on data from several years later under the assumption that patterns of emission had not changed during those years. Both remaining studies used monitors to determine exposure concentrations, which presented issues similar to studies of $PM_{2.5}$ mass, where subjects are limited to those women living within a certain distance of the monitors, or within a city with a relatively dense monitoring network.

Exposure assignment is based on maternal residence at birth. If women spend much of their time outside of their homes in locations where the air environment is substantially different or move during pregnancy between areas with different exposure levels, exposure could be misclassified. Assignment based on maternal residence at birth may be a larger problem in studies that employ LUR or similar models, as these are more spatially resolved.(Wu et al. 2009) In the case of particulate matter, it is likely that exposure misclassification is nondifferential. Therefore, any bias introduced will probably be toward the null. With the small effect sizes seen in risk of PTB, $PM_{2.5}$ or its species may be falsely deemed unimportant.

Another area in which more exploration could be useful is the examination of preterm birth as more than a single outcome. Currently, it is customary to look at births as either term or preterm. However, the births considered preterm are far from homogeneous. Preterm birth covers 16 weeks of pregnancy, nearly half of a full term

pregnancy, and development occurs rapidly during this time. The health of a child born at 25 weeks completed gestation can be very different than one born at 35 weeks completed gestation. Those pregnancies ending in the earliest preterm weeks are also those with the most severe health outcomes and lifetime costs and consequences. It is plausible that there are different underlying etiologies of birth across the 4 month period of gestation, and these potential differences should be considered when examining preterm birth as an outcome of interest.

Effects of $PM_{2.5}$ have been found for multiple windows of exposure in studies of preterm birth, and no one exposure period stands out as definitive. Researchers investigated preterm birth in association with exposure to $PM_{2.5}$ and specific species for exposure in early, middle, and late pregnancy and acute (1-3 days), monthly, trimester, and whole pregnancy exposures. The exploration of small windows of exposure anchored at specific gestational ages may aide in highlighting periods of vulnerability during gestation.

2.6 Public health significance

The potential for harmful reproductive health outcomes due to $PM_{2.5}$ exposure exists even below the current standards. Investigation into health effects at levels ranging below regulatory standards may demonstrate the need to continue lowering $PM_{2.5}$ standards for the protection of health. Even with demonstrated adverse health effects, ambient levels of $PM_{2.5}$ may yet be above regulatory standards, e.g. in 2006 23 PA, 15 NJ, and 8 OH counties were classified as above acceptable levels.(USEPA 2010d) Further evidence of adverse health outcomes of $PM_{2.5}$ at these levels and below gives

more weight to regulatory standards. In addition, information on the contributions of $PM_{2.5}$ species to health effects remains limited. Should one or more $PM_{2.5}$ species emerge as particularly associated with adverse health effects, then regulations may be targeted at that (or those) species. Increasing the base of knowledge on this subject allows for more informed decision making when setting new regulatory standards, including information on pregnant women and infants as a potentially vulnerable subpopulation.

Preterm birth captures a 4 month period across pregnancy. By examining categories of PTB, rather than PTB as a single outcome, we can detect associations specific to each gestational age. These associations may not be distinguishable when examining the entire 4 month preterm period, and their detection can impact our understanding of the etiology and long term health effects of preterm birth. This understanding in turn provides better information for basing policies related to air pollution control.

Over the 4 month period considered preterm, fetal development is occurring rapidly.

Even small increases in risk can have a large impact on some groups, such as the earliest preterm births, who experience extensive morbidity and associated costs even compared to later preterm births.(Behrman and Butler 2007)

Evaluating risks for specific weeks of gestation also allows for detection of associations that may not be distinguishable when examining the entire 4 month preterm period.

Our study assists in examining associations with $PM_{2.5}$ at or below current regulatory standards, identifying the species of $PM_{2.5}$ that may be more responsible for adverse health effects, and examining potential differences in effect of $PM_{2.5}$ with preterm birth at varied gestational ages.

Chapter 3: Methods

Table 3.1: Overview of study design, aim 1 & aim 2

Design	Cohort
Eligibility	Births at risk of PTB from Jan 1, 2000 to Dec 31st 2005 to women living in PA, NJ, OH.
Sample Size	1,781,527
Outcome	Extremely preterm birth (ExPTB): 20-27 completed gestational weeks Very preterm birth (VPTB): 28-31 completed gestational weeks Moderate preterm birth (MPTB): 32-34 completed gestational weeks Late preterm birth (LPTB): 35-36 completed gestational weeks
Outcome data source	Birth certificates for PA, NJ, OH from 2000 to 2005
Exposure, weekly average	$PM_{2.5}$ mass $PM_{2.5}$ sulfate (SO_4) $PM_{2.5}$ nitrate (NO_3) $PM_{2.5}$ organic carbons (OC) $PM_{2.5}$ elemental carbon (EC)
Exposure data source	Community Multi-scale Air Quality (CMAQ) model, bias-corrected with monitor data
Spatial resolution	12 km grids
Assigning exposure	Maternal residence at birth linked to grid
Exposure Windows	Each week of gestation from "time of conception" to birth Weeks lagged from birth, up to 8 weeks
Covariates	Maternal demographics Co-pollutants
A priori modifiers	Parity (primiparous v. multiparous) Infant sex (male v. female) Maternal smoking status (smoker v. non-smoker) Maternal race (black v. non-black)
Analytic approach	Modified Poisson linear risk regression
Effect measures estimated	Risk differences (RD) per 1,000,000 pregnancies

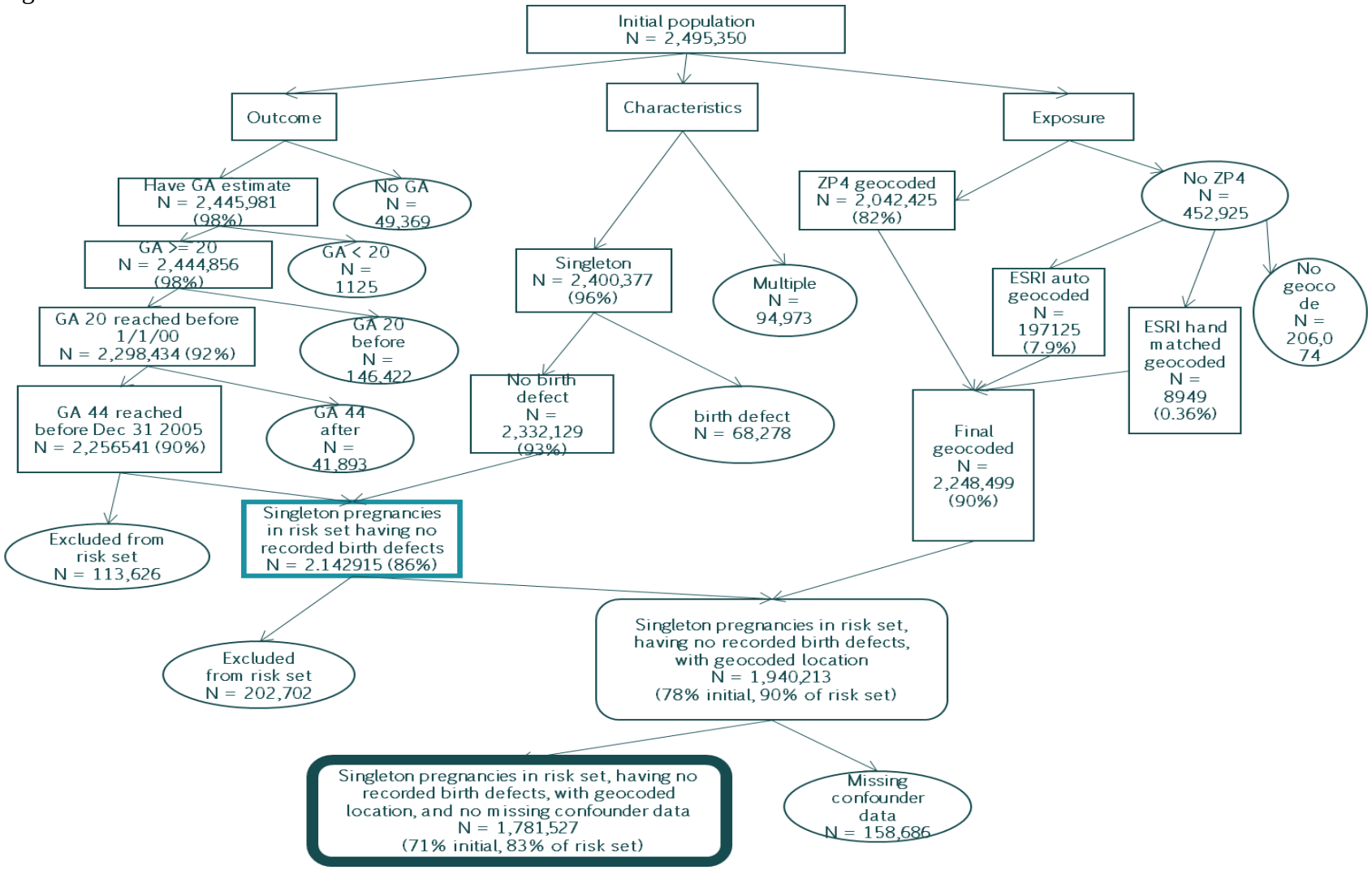
This study focuses on assessing the relationships between exposure to $PM_{2.5}$ mass and $PM_{2.5}$ species and the risk of preterm birth at specific gestational weeks. To answer these questions we assembled a cohort of pregnancies from Pennsylvania, Ohio, and New Jersey for 2000 to 2005. Preterm birth, based on clinical estimate of gestational age as recorded on the birth certificate, was split into four categories: extremely preterm birth (ExPTB) at 20-27 completed gestational weeks; very preterm birth (VPTB): 28-31 completed gestational weeks; moderate preterm birth (MPTB): 32-34 completed gestational weeks; and late preterm birth (LPTB): 35-36 completed gestational weeks. Maternal residences at birth were geocoded and linked to CMAQ grids. Concentrations for each day of pregnancy were assigned for $PM_{2.5}$ mass, EC, OC, SO_4, NO_3, and ozone), then averaged over fixed 7 day periods to produce weekly exposures. Using knowledge from literature reviews and field experts, a directed acyclic graph was constructed and analyzed to determine a minimally sufficient adjustment set of demographic factors (e.g., maternal race, maternal education, maternal age at delivery, and maternal marital status) and co-occurring ozone. Risk differences were estimated for exposures at each week of gestation anchored at conception, and for up to 8 lagged weeks anchored at birth, using modified Poisson regression adjusting for demographic factors, and with and without co-occurring ozone. Finally, effect measure modification by race, smoking status, infant sex, and maternal parity was examined.

3.1 Study population

Live birth records provided by the state health departments of Pennsylvania (PA), New Jersey (NJ), and Ohio (OH) were used to construct a cohort of fetuses reaching at

least 20 weeks gestation. The three states were chosen as the study location because both spatial and temporal gradients of $PM_{2.5}$ are available over this area. This cohort consisted of those fetuses that were at risk of preterm birth (completed gestational weeks 20-36) for the period between 1 January 2000 and 31 December 2005. Pregnancies were restricted to those having achieved gestational week 20 no earlier than 1 January 2000, and gestational week 45 no later than 31 December 2005. This was done to address the possibility of fixed-cohort bias, wherein differing lengths of gestation between term and preterm births might lead to exposure artifacts.(Strand et al. 2011) We then restricted the population to singleton pregnancies with no known congenital anomalies. A point-geocodeable (latitude and longitude assignable) maternal residence was also required. Exclusions and cohort construction are shown in figure 2. These restrictions left an eligible population of 1,940,213 pregnancies, of which 1,781,527 were missing no major covariate (e.g., race, education, maternal age, marital status) information.

Figure 3.1: Flow chart of cohort creation



3.2 Outcome assessment

Gestational age was determined by clinical estimate of gestational age as reported on birth certificates. Combined measures substituting last menstrual period gestational age when clinical estimate was missing were not used due to concerns of differing distributions and therefore biases between the two.(Wingate et al. 2007) Preterm birth status was defined as having a gestational age between 20-36 completed weeks; term birth status was defined as having a gestational age between 37-45 weeks. PTB was further subset into four categories based on definitions from the World Health Organization(WHO 2012): extremely PTB (ExPTB) gestational age between 20-27 weeks; very PTB (VPTB) gestational age between 28-31 weeks; moderate PTB (MPTB) gestational age between 32-34 weeks; and late PTB (LPTB) gestational age of 35-36 weeks. These categorizations were made to better elucidate the severity of health response and the potential for variety of response to exposure based on gestational age, as development occurs rapidly during this period and the full range of PTB covers 4 months of gestation, and during the different developmental stages the growing fetus may be differently vulnerable to insult.

3.3 Exposure assessment

As a brief overview, exposures used in this analysis were average weekly concentrations for each week of pregnancy anchored at conception and average weekly concentrations lagged from birth up to 8 weeks (i.e., week of birth, 1 week before birth, …8 weeks before birth). To assign exposures, maternal residence at birth was geocoded and linked to the CMAQ grid in which it fell. Each day of pregnancy for each woman

was then matched to concentration values for that day. Finally, daily concentrations were averaged over fixed 7-day periods to estimate weekly average concentrations. These weekly average concentrations were then used in regression models.

3.3.1 Geocoding

Maternal addresses from all birth records were cleaned and standardized using the ZP4 address correction software (version expiring 1 May 2012; Semaphore Corporation, Monterey, CA, USA) with Delivery Point Validation (DPV) and Locatable Address Conversion System database ($LACS^{link}$), which enhance address validation and allows conversion between address styles (e.g., rural routes to street names) respectively. The ZP4 geographic database add-on was used to assign latitude and longitude values based on the Census Bureau's Topologically Integrated Geographic Encoding and Referencing system (TIGER) street segments (n=2,042,425). Those addresses that did not receive latitude and longitude values (n=452,925) were then geocoded using ArcGIS online geocoding service in ArcMap 10 (ESRI, Redlands CA), which returns a matching location, a tied location, or unmatched status. 197,125 addresses returned as matched; 8949 addresses returned as tied and were hand match to the best candidate. This process resulted in 2,248,499 pregnancies having latitude and longitude values within the study area. This dataset was then merged with the study population dataset for the final eligible study population of 1,940,213 pregnancies to which exposure could be assigned (Figure 2).

Modeled and measured PM data were merged using the combined model-observational approach: to construct PM exposure measures, output from the Community

Multiscale Air Quality (CMAQ) model were adjusted based on measured data collected from the Chemical Speciation Network (CSN) and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network (Figure 3).(Hogrefe et al. 2009) Estimated concentrations of $PM_{2.5}$ and its constituent species [sulfate (SO_4), nitrate (NO_3), ammonium (NH_4), elemental carbon (EC), organic carbon (OC), and crustal/other PM] were provided in 12 km grids.(Hogrefe et al. 2009) This section offers an overview of the components of the combined model-observational approach and how the exposure metric is produced.

3.3.2 Particulate matter

Daily estimated concentrations of $PM_{2.5}$ were provided by the EPA's Atmospheric Exposure Integration Branch in the National Exposure Research Laboratory for 1999 to 2005 in 12x12 km grid. These estimates were constructed using output from the CMAQ model bias-corrected with monitoring network data, as detailed in Hogrefe et al.(2009) Briefly, meteorological conditions and criteria pollutant emissions are input into CMAQ, which simulates chemical and physical processes and chemical transport occurring in the atmosphere, then estimates gridded concentrations of ambient air pollutants.(Byun and Schere 2006; Hogrefe et al. 2009) Baseline concentrations of $PM_{2.5}$ were created by matching grids to monitoring sites and applying a Kolmogorov–Zurbenko (15,5) moving average filter. Adjustment factors were then created as the ratio of observed to modeled concentrations, spatially interpolated across the gridded field.(Hogrefe et al. 2009) CMAQ output was then multiplied by the appropriate adjustment factors to produce the final bias-corrected concentration estimates.

3.3.2.1 Community Multiscale Air Quality modeling system

Unlike monitoring data, the CMAQ model has the ability to simulate concentrations at hourly or daily temporal scales, and covers a vast spatial domain.(Marmur et al. 2004) CMAQ is constructed with inputs from meteorological conditions and criteria pollutant emissions. Temperature, humidity, air flow and other meteorological conditions were simulated using the National Center for Atmospheric Research/Penn State Mesoscale Model (MM5). The MM5 consists of several programs and interpolates both horizontal and vertical meteorological data.(Grell et al. 1994; NCAR 2003) More information on the processes of this model can be found at http://www.mmm.ucar.edu/mm5/mm5-home.html.

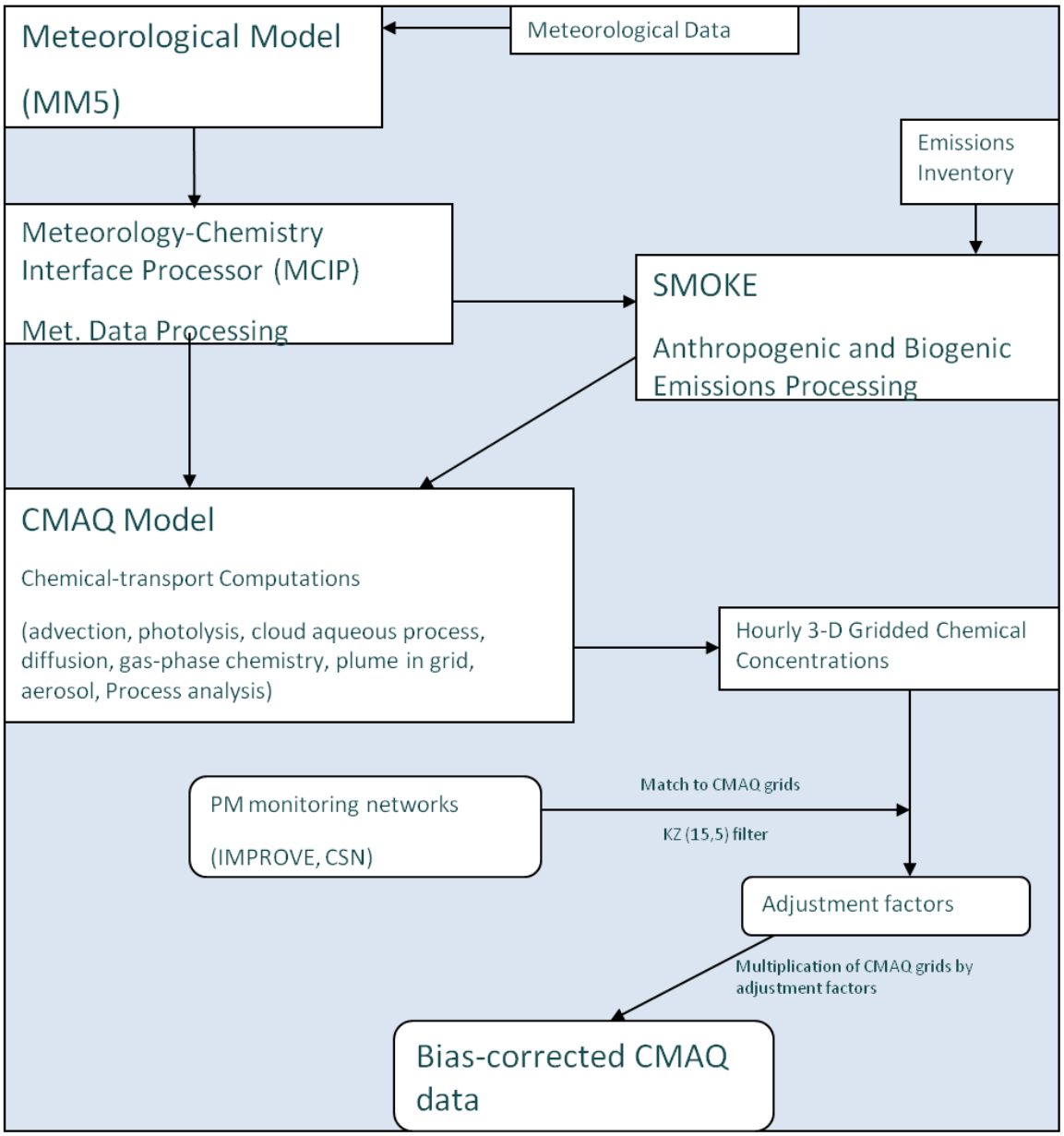


Figure 3.2: Flowchart of combined model-observational approach showing components of the CMAQ modeling system and process of fusing data. Adapted from Byun & Schere 2006, Hogrefe et.al. 2009, and the Summary Report of the Atmospheric Modeling and Analysis Research Activities for 2008.(Byun and Schere 2006; Hogrefe et al. 2009; USEPA 2010c)

Criteria pollutant emissions were collected or estimated from several sources. Emissions from vegetation and soils were estimated using the Biogenic Emissions Inventory System (BEIS3.12).(Hogrefe et al. 2009; USEPA 2010b) For year 2000 and

before, Hogrefe et al.(2009) used the U.S. EPA National Emission Trends database: point source emissions were modeled on the available stack-level inventories and mobile source emissions were estimated using annual vehicle miles traveled and temperature. For 2001, Hogrefe et al.(2009) used the anthropogenic emission inventories prepared for the EPA Clean Air Interstate Rule.(USEPA 2010a) Finally for 2002 to 2005, emissions inventories for year 2002 and 2009 prepared for the Ozone Transport Commission were used either directly or to estimate emission inventories through linear interpolation.(Hogrefe et al. 2009) Once collected, all emissions were processed in the Sparse Matrix Operator Kernel Emissions (SMOKE) system. SMOKE is an emissions processor designed to transform emissions inventory data—usually in annual-total emissions—through temporal allocation, chemical speciation, and spatial allocation while controlling for emission source, for further use in air quality modeling.(Houyoux et al.)

Simulated metrological conditions and collected emissions inventories were input into the CMAQ model, version 4.5.1.(Byun and Schere 2006) The CMAQ modeling system simulates chemical and physical processes and chemical transport occurring in the atmosphere. It then estimates gridded concentrations of ambient air pollutants.(Byun and Schere 2006; Hogrefe et al. 2009).

3.3.2.2 Bias correction with monitoring data

For bias correction, CMAQ output grids were matched to monitors in the Chemical Speciation Network (CSN) and the Interagency Monitoring of Protected Visual Environments (IMPROVE) network.(Hogrefe et al. 2009) To calculate baseline concentrations of $PM_{2.5}$ mass and species, the modelers applied a Kolmogorov–Zurbenko

(KZ) (15,5) moving average filter.(Hogrefe et al. 2009) The KZ filter provides separation of frequencies through relatively simple algorithm and preserves true information when used with unevenly spaced or missing data.(Rao et al. 2003) This method returned daily estimates, even with measurements being available only every 3rd or 6th day, as $PM_{2.5}$ measurements are.(Hogrefe et al. 2009) The six daily values were then averaged for each day, and for each day for each species for each monitor the modelers calculated the ratio of observed to modeled average seasonal baseline as an adjustment factor.(Hogrefe et al. 2009) As the adjustment factor could only be created in grids with co-located monitors, a gridded map of adjustment factors was then created through spatial interpolation. Finally, the CMAQ output was multiplied by the appropriate adjustment factor to produce bias-corrected concentration estimates.

Bias-corrected estimates were then evaluated against the original 12 km gridded CMAQ output through comparisons to 24-hour $PM_{2.5}$ mass measurements at Federal Reference Method monitors.(Hogrefe et al. 2009) In general, the fused estimates had lower root mean squared errors and higher correlations with observed measurements than the original CMAQ, indicating a generally improved performance.(Hogrefe et al. 2009) The performance of the model was most improved in the urban corridor between Washington, DC and New York City.(Hogrefe et al. 2009)

This method improves upon the uncorrected CMAQ estimates of $PM_{2.5}$ mass and species concentration, and provides estimates for times and locations that do not have available measured data. Limitations remain in that the spatial resolution of the model does not go below 12 km grids, and the performance of the model varies by species.(Hogrefe et al. 2009) For example, the model is known to underestimate OC

concentration. Uncertainty in the model's estimation may be due to differences in the method of measuring OCs between monitoring sites and networks. As well, CMAQ is thought to be missing sources of OC, particularly secondary OC formed through atmospheric processes.(Hogrefe et al. 2009) Though the fused model's estimations are imperfect, it improves upon CMAQ predictions of OC. The spatial resolution of the model means that small spatial scale changes in concentrations (e.g., due to traffic gradients) will not be apparent. Figure 4 shows a spatial gradient of $PM_{2.5}$ using the bias-corrected CMAQ for a day during the study period.

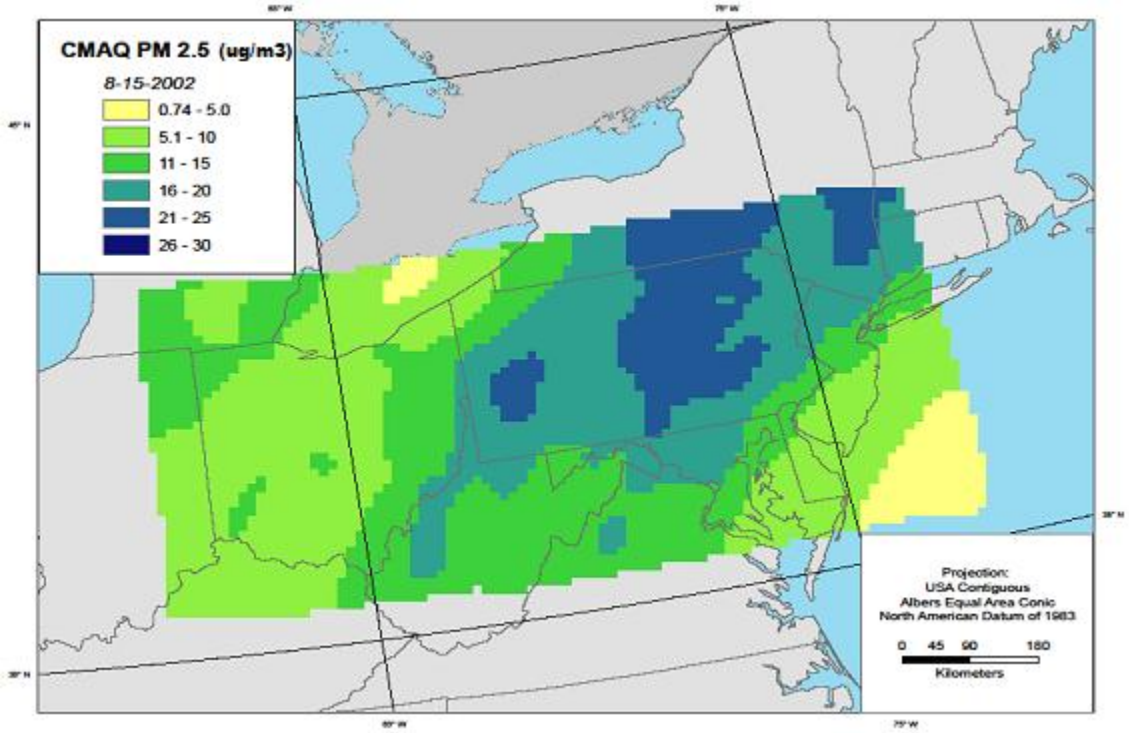


Figure 3.3: $PM_{2.5}$ mass concentration as predicted by the fused CMAQ model for 8/15/2002. Shown across OH, PA, and NJ.

3.3.3 Assigning PM to pregnancy and creation of exposure windows

Daily values for $PM_{2.5}$ mass and species exposure were assigned to pregnancies by matching geocoded maternal residential location to CMAQ grid. Start date of pregnancy ("time of conception") was calculated by subtracting clinical estimate of

completed gestational weeks from date of birth, and dates for each day from the calculated start of pregnancy to birth were matched to date of CMAQ concentration estimation. Exposure was assigned in two ways (Figure 4). First, we assigned exposure anchored from the time of conception. $PM_{2.5}$ concentrations were averaged over fixed seven day periods of gestation to estimate weekly average concentrations (i.e., average of days 1-7 equals concentration for week 1, average of days 8-14 equals concentration for week 2, etc.) for all pregnancies. These exposure windows were the same for all pregnancies, not dependant on gestational age at birth. Second, we assigned exposure windows anchored at birth (lagged windows of exposure). We lagged fixed windows of 7–day exposures from birth and assigned average $PM_{2.5}$ concentrations for each week. The lag refers to time from birth; all exposures are a one-week average $PM_{2.5}$ concentration (non-cumulative). For example, for a birth occurring at week 32, a two week lagged exposure would reflect exposure for gestational week 30. While a birth occurring at week 44, a two week lagged exposure would reflect exposure for gestational week 42. Average weekly $PM_{2.5}$ concentrations anchored at birth were assigned for lags up to eight weeks from birth.

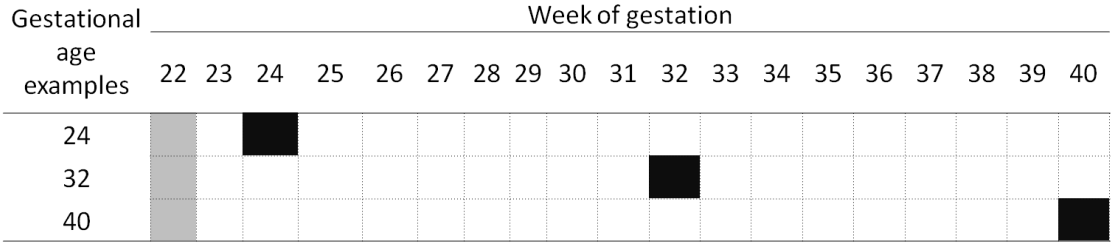


Figure 3.4: Examples of possible exposures at gestational week 22 and with a lag of 0 from birth, for pregnancies with gestational ages of 24, 32, and 40 weeks.

3.4 Covariate assessment

To achieve a least biased estimate of association, a directed acyclic graph (DAG) was constructed based on literature review and knowledge of preterm birth risk factors and factors affecting $PM_{2.5}$ (Figure 5). For preterm birth, the literature review was focused on overviews of the epidemiology of preterm birth and on the Institute of Medicine report convened in part to review and report on the causes of preterm birth.(Behrman and Butler 2007) This report reviewed all extant literature and provided expert analysis of evidence for each determined cause of preterm birth. For factors affecting particulate matter, we relied upon consultation with air pollution experts at the U.S. EPA as well as review of literature detailing conditions of $PM_{2.5}$ formation and propagation in the environment.(NARSTO 2004; U.S.EPA. 2009) We considered confounders to be those variables that were risk factors for preterm birth and independently associated with $PM_{2.5}$, while not being affected by either preterm birth or $PM_{2.5}$.(Greenland et al. 1999) In the construction of the DAG, risk factors for preterm birth were evaluated for their potential influence on maternal residence, as this will in turn be associated with a woman's $PM_{2.5}$ exposure due to the way exposure was assigned. Risk factors for preterm birth representing socioeconomic status (SES) were considered to have a direct link to maternal residence (e.g., race, educational attainment, marital status, and age at delivery).(Behrman and Butler 2007; Berkowitz and Papiernik 1993; Goldenberg et al. 2008; Martin et al. 2007; Mathews and MacDorman 2010) Other risk factors for preterm birth had indirect links to residence through socioeconomic factors (e.g., smoking status, prenatal care in early pregnancy, and parity). Risk factors for preterm birth also had links between themselves (e.g., race is associated with smoking

status and educational attainment). The links between factors associated with $PM_{2.5}$ exposure and preterm birth are somewhat more tenuous, with the literature being either mixed or with few to no studies. Other co-pollutants, ozone (O_3) in particular, have been linked to preterm birth and co-occur temporally and spatially with $PM_{2.5}$.(Lee et al. 2012; Olsson et al. 2013) Effects of $PM_{2.5}$ are often evaluated with and without adjustment for O_3, offering additional reason to include it in our models. Other factors, such as season and temperature, are certainly associated with $PM_{2.5}$ exposure, but their association with preterm birth is somewhat questionable. Due to their tenuous connection with preterm birth, these factors were only included in sensitivity analyses, not in the DAG. After construction of the DAG was complete, it was analyzed and minimally sufficient adjustment sets were identified using the DAG Program.(Knuppel and Stang 2010) Identified covariates included maternal race (non-Hispanic white, non-Hispanic black, Hispanic, other), maternal education level (<8^{th} grade, some high school, high school diploma, some college, Bachelor's degree, Graduate schooling), marital status (married, unmarried), maternal age at delivery (restricted quadratic splines), and ozone**.** Individual characteristic data was extracted from birth certificates, while ozone data was obtained from CMAQ models and exposure estimated in a similar manner to $PM_{2.5}$ (Table 4).

3.5 Effect measure modifiers

Potential effect measure modifiers (EMM; i.e., factors for which the effect of exposure differs by level) identified a priori included race (black, non-black), smoking status (smoker, non-smoker), infant sex (male, female), and maternal parity (primiparous, multiparous).

Race was investigated as an EMM, not because of biological effects, which are unlikely, but due to the possibility that race serves as a proxy for social stressors that may prime women for or exacerbate the effects of exposure to $PM_{2.5}$ (i.e., synergistic effects).(Kaufman et al. 1997; Kaufman 2008) In other words, social stressors related to race in the United States may create an "allostatic load" in which a woman has long term biological dysregulation due to the continuous or frequently occurring presence of stressors.(McEwen and Seeman 1999) This allostatic load then prevents women from responding appropriately (in a biologic sense) to further stressors such as air pollutants. Smoking affects risk of preterm birth and may also prime women for effects of exposure to $PM_{2.5}$, or effects of smoking may cause effects of $PM_{2.5}$ exposure to be washed-out (i.e., antagonistic effects). Infant sex was examined because male and female fetuses may have alternate developmental trajectories in utero, as evidenced by birth weight distributions,(Wilcox 2010) and may experience the effects of $PM_{2.5}$ differently. Parity will be investigated due to speculation that parous women may be less likely to move during pregnancy or more likely to stay at home with older children, thus improving exposure classification.(Madsen et al. 2010; Ritz et al. 2007; Ritz and Wilhelm 2008)

Table 3.2: Confounders and effect measure modifiers of the relationship between particulate matter and preterm birth

Variable	Rationale	Data source	Classification
Maternal education level	Factors related to social class and economic status may influence the location of maternal residence. Some may also serve as proxies for unmeasured social/cultural factors.	Birth certificate	Confounder
Maternal Race/ethnicity		Birth certificate	EMM/Confounder
Marital status		Birth certificate	Confounder
Parity		Birth certificate	EMM
Maternal age at birth		Birth certificate	Confounder
Maternal smoking status		Birth certificate	EMM
Infant sex	Male and female fetuses may experience different risks	Birth certificate	EMM
Ozone	Shares sources with PM and shows some association with PTB	CMAQ	Confounder
Maximum temperature	Contributes to formation of PM	CMAQ	Confounder?
Season (of conception)	Seasonality in PM	Birth certificate	Confounder?

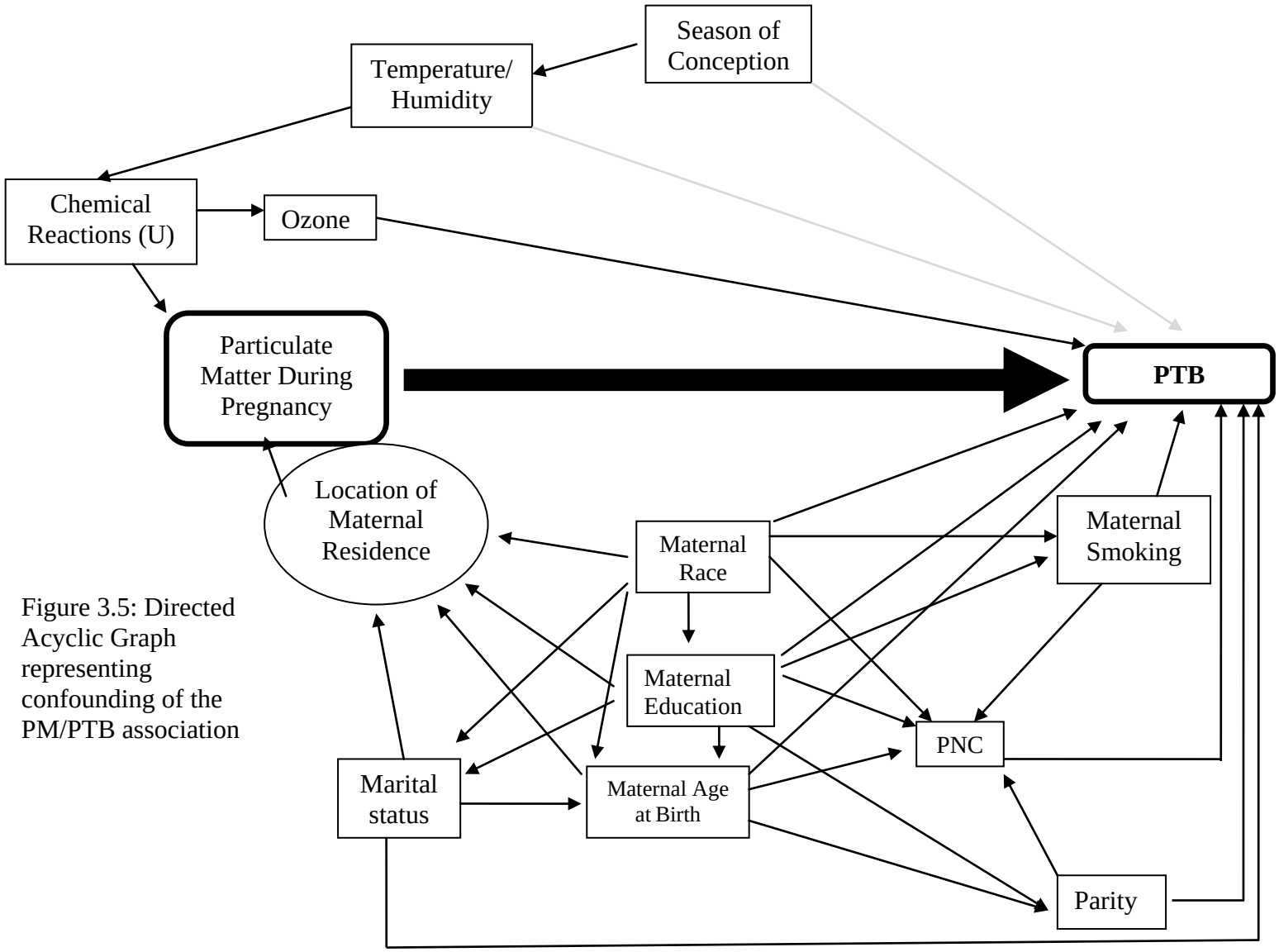


Figure 3.5: Directed Acyclic Graph representing confounding of the PM/PTB association

3.6 Data analysis

The univariate distribution of all variables included in the analysis was examined using frequencies and percents for categorical variables, and descriptive statistics (e.g., mean, median, standard deviation, etc) for continuous variables, including temporal and between-pollutant correlations for $PM_{2.5}$ mass, $PM_{2.5}$ species, and O_3. Number and percent of missing data was also evaluated for each variable. Variables with out-of-range or impossible values (e.g., gestational age <20 completed weeks) were set to missing.

Risk differences (RD) were estimated using single and multi-variable modified Poisson regression with an identity link.(Spiegelman and Hertzmark 2005; Zou 2004) The modified Poisson regression was used as binomial regression would induce heteroskedasticity. Each category of preterm birth (ExPTB, VPTB, MPTB, LPTB) was used as a dichotomous outcome in separate models. $PM_{2.5}$ mass, $PM_{2.5}$ species, and O_3 were treated as continuous variables. Individual models were produced for exposure during each week of gestation and for each lagged week. Two sets of adjusted models were created: models adjusted for demographic characteristics, and models adjusted for co-occurring ozone. In addition, for $PM_{2.5}$ species analysis models were performed with a single $PM_{2.5}$ species or with all four $PM_{2.5}$ species. Effect measure modification was evaluated by including interaction terms for each potential modifier and continuous $PM_{2.5}$ mass or species, and performing -2 log likelihood tests with a significance level of $p<0.05$ due to the large population. All analyses were performed using SAS version 9.3 (Cary, NC).

3.7 Sensitivity analyses

For risks with exposure to $PM_{2.5}$ mass, modification by state of residence was evaluated, because of the potential for differing $PM_{2.5}$ composition by area. Models were also run with adjustment for maximum temperature (from CMAQ models, continuous) at time of exposure, and with season of conception, as these factors may be potential confounders, though not identified though our DAG analyses.

3.8 Interpretation of effects

In this analysis we are not performing hypothesis testing but describing associations and providing estimates of precision/quantification of the potential for random bias around those associations. As such, interpretation of risk differences as "positive", "null", or "negative" was based not on "statistical significance" but on the authors' judgement not only of the meaning of individual associations but of patterns of association. For example, risks that were elevated or displayed gradual elevation across exposure windows were more likely to be interpreted as meaningfully positive risks, whereas a single elevated risk with confidence limits above the null would not necessarily be interpreted as positive if the risks in near exposures windows were null.

We also present both marginal and stratified risk differences for exposures that show evidence of effect measure modification. Marginal effects are effectively standardized to the population distribution, reflecting the overall impact of air pollution, and are most likely those on which general regulatory judgments will occur (air pollution must be regulated for all, cannot specify a subgroup to reduce exposure for). With the presence of effect measure modification, potentially vulnerable subgroups are identified

and highlighted. Stratified effects also have regulatory utility, in that regulations may not be specific to a group of people, but the levels at which air pollution is permitted may be set with a vulnerable subgroup in mind.

3.9 Required Approvals

This research was approved by the University of North Carolina at Chapel Hill's Office of Human Research Ethics (Study # 11-1089), the Pennsylvania Department of Health Bureau of Health Statistics & Research (# 1C-2460), New Jersey Department of Health and Senior Services Institutional Review Board (#0379), and the Ohio Department of Health Human Subjects Institutional Review Board (# 2011-16).

Chapter 4: Exposure to particulate matter during pregnancy and risk of birth at preterm gestational ages

4.1 Overview

Particulate matter has been variably associated with preterm birth (PTB). We estimated risk of birth in four preterm categories (risks reported as PTBs per 10^6 pregnancies; PTB categories = 20-27; 28-31; 32-34; and 35-36 weeks completed gestation) and risk differences (RD (95% confidence intervals)) for PTB categories with change in ambient concentrations of PM <2.5 micrometers in aerodynamic diameter ($PM_{2.5}$). From live birth certificates with clinical estimate of gestation and date of delivery, we constructed a 20-week gestational age cohort of singleton pregnancies in 2000-2005 (n=1,940,213; 8% PTB (approximately 80,000 per 10^6 for all categories)). We estimated mean $PM_{2.5}$ exposures for each week of gestation from monitor-corrected Community Multi-Scale Air Quality modeling data. RDs were estimated using modified Poisson linear regression, adjusted for maternal race, marital status, education, age, and ozone. RD estimates varied by exposure window and outcome period. Exposure to $PM_{2.5}$ at week four of gestation resulted in generally elevated risks, though magnitude varied by PTB category (e.g., for a 1μg/m^3 increase RD=11.8(-6, 29.2); RD=46(23.2, 68.9); RD=61.1(22.6, 99.7); and RD=28.5(-39, 95.7) for birth at weeks 20-27, 28-31, 32-34, and 35-36 respectively). Exposures anchored at time of birth were associated with positive RDs for lags of 0-2 weeks across PTB categories. Conclusions: Exposures beginning around the time of implantation and near birth appear to be of particular

importance. Because particulate matter exposure is ubiquitous, observation of any effect on PTB, even of small magnitudes, carries potential for harm.

4.2 Background

Particulate matter under 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$), one of the criteria air pollutants regulated under the Clean Air Act, is a complex mixture of extremely small particles and liquid droplets. Levels of $PM_{2.5}$ vary across the United States and are often below EPA standards, everyone is exposed to some extent. $PM_{2.5}$ has been associated with a number of adverse health outcomes, including cardiovascular mortality, asthma, and poor pregnancy outcomes.(Backes et al. 2013; Dominici et al. 2003a; Dominici et al. 2006; Lewtas 2007; U.S.EPA. 2009) Of the pregnancy outcomes studied in conjunction with PM exposure, PTB is an important outcome because it is not only a marker for fetal underdevelopment but also a risk factor for further adverse health outcomes, such as infant mortality, neurodevelopmental problems, and growth issues.(Behrman and Butler 2007; Gilbert et al. 2003; Mathews and MacDorman 2010; Saigal and Doyle 2008) Findings for studies of $PM_{2.5}$ and PTB have generally been positive for whole pregnancy exposure and for exposures in the first trimester and late in pregnancy,(Brauer et al. 2008; Chang et al. 2012; Gehring et al. 2011; Huynh et al. 2006; Lee et al. 2012; Warren et al. 2012; Wilhelm et al. 2011; Wu et al. 2009; Wu et al. 2011) though some studies have found null or protective effects of $PM_{2.5}$ on PTB.(Darrow et al. 2009; Gehring et al. 2011; Jalaludin et al. 2007; Wilhelm and Ritz 2005) Variation in findings may be due in part to differences in study designs, populations, or exposure metrics and contrasts. These studies have primarily relied upon air pollutant monitoring

for exposure assignment; this by necessity limits inclusion to those women residing close to these monitors during pregnancy. Moreover, monitors may not be active at all times, potentially leading to exclusions based on unmonitored time periods. Previous studies have focused on any birth between 20-36 weeks as their outcome and examined exposure windows of at least one month or trimester in length (somewhat due to reliance on monitoring data), when there may be shifts in vulnerability based on gestational age and critical windows of vulnerability may be much shorter. Pregnancies ending in the earliest preterm weeks are also those with the most severe health outcomes and lifetime costs and consequences. It is plausible that there are different underlying etiologies of birth across the four month period of gestation, and these potential differences should be considered when examining preterm birth as an outcome of interest.

In this study, we examine the association between ambient $PM_{2.5}$ and risk of PTB using a 20-week gestational cohort across six years and three states. We employ the EPA's Community Multiscale Air Quality (CMAQ) model, which offers complete spatial coverage and daily estimated air pollutant concentrations, leading to a more extensive study area and therefore population. We estimate risk differences for $1\mu g/m^3$ increases in average weekly $PM_{2.5}$ exposure at each week of gestation and birth at four categories of preterm gestation.

4.3 Methods

Study population

Live birth records provided by the State Health Departments of Pennsylvania (PA), New Jersey (NJ), and Ohio (OH) were used to construct a 20-week gestational

cohort. This cohort consisted of those fetuses that were at risk of preterm birth for the period between 1 January 2000 and 31 December 2005. The three states were chosen as they either have similar source profiles for $PM_{2.5}$ or regional sources are a large contributor to PM profiles.(U.S.EPA.) From all birth records (n=2,495,350) the study population was restricted to the following: singleton pregnancies with no recorded birth defects, with an estimated gestational age available, and having achieved gestational week 20 no earlier than 1 January 2000 and gestational week 45 no later than 31 December 2005 (birth dataset, n=2,142,915/ number excluded = 352,435). A point-geocodeable (latitude and longitude assignable) birth address was also required (excluded n=202,702). These restrictions lead to a final study population of 1,940,213 pregnancies

Gestational age, pregnancy start, and preterm birth status

Gestational age was determined by clinical estimate of gestational age as reported on birth certificates. Start date of pregnancy (time of conception) was calculated by subtracting clinical estimate of completed gestational weeks from date of birth. Preterm birth status was defined as having a gestational age between 20-36 completed weeks. PTB was further subset into four categories based on World Health Organization definitions and literature review: extremely PTB (ExPTB) gestational age between 20-27 weeks; very PTB (VPTB) gestational age between 28-31 weeks; moderate PTB (MPTB) gestational age between 32-34 weeks; and late PTB (LPTB) gestational age of 35-36 weeks. Term births were births between 37-45 completed gestational weeks. These categorizations were made to better elucidate the severity of health response and the potential for variety of response to exposure based on gestational age, as development

occurs rapidly during this period and the full range of PTB covers 4 months of gestation, and during the different developmental stages the growing fetus may be differently vulnerable to insult.

Exposure data

Maternal address data was taken from all birth records and processed with the Zp4 address locator program (Semaphore Corporation, Monterey CA) to assign latitude and longitude values to the address based on TIGER street segments (n=2,042,425). Those addresses that did not receive latitude and longitude values (n=452,925) were then geocoded using ArcGIS online geocoding service in ArcMap 10 (ESRI, Redlands CA), which returns a matching location, a tied location, or unmatched status. 197,125 addresses returned as matched; 8949 addresses returned as tied and were hand match to the best candidate. This process resulted in 2,248,499 pregnancies having latitude and longitude values. The birth and location datasets were then merged together for a final study population of 1,940,213 pregnancies.

Daily estimated concentrations of $PM_{2.5}$ were provided by the EPA's Atmospheric Exposure Integration Branch in the National Exposure Research Laboratory for 1999 to 2005 in 12 km grids. These estimates were constructed using output from CMAQ model bias-corrected with monitoring network data, as detailed in Hogrefe et al.(Hogrefe et al. 2009) Briefly, meteorological conditions and criteria pollutant emissions are input into CMAQ, which simulates chemical and physical processes and chemical transport occurring in the atmosphere, then estimates gridded concentrations of ambient air pollutants.(Byun and Schere 2006; Hogrefe et al. 2009) Baseline concentrations of $PM_{2.5}$

were created by matching grids to monitoring sites and applying a Kolmogorov–Zurbenko (15,5) moving average filter. Adjustment factors were then created as the ratio of observed to modeled concentrations, spatially interpolated across the gridded field.(Hogrefe et al. 2009) CMAQ output was then multiplied by the appropriate adjustment factors to produce the final bias-corrected concentration estimates.

Daily values for pollutant exposure were assigned to pregnancies by matching geocoded maternal residential location to CMAQ grid. Dates for each day from the calculated start of pregnancy to birth were matched to date of CMAQ concentration estimation. Exposure was assigned in two ways. First, we assigned exposure anchored from time of conception. $PM_{2.5}$ concentrations were averaged over fixed seven day periods of gestation to estimate weekly average concentrations (i.e., average of days 1-7 equals concentration for week 1, average of days 8-14 equals concentration for week 2, etc) for all pregnancies. Second, we assigned exposure windows anchored at birth (lagged windows of exposure). We lagged fixed windows of 7–day exposures from birth and assigned average $PM_{2.5}$ concentrations for that week. The lag refers to time from birth; all exposures are a one-week average $PM_{2.5}$ concentration (non-cumulative). For example, for a birth occurring at week 32, a two week lagged exposure would reflect exposure for gestational week 30. While a birth occurring at week 44, a two week lagged exposure would reflect exposure for gestational week 42. Average weekly $PM_{2.5}$ concentrations anchored at birth were assigned for lags up to eight weeks from birth.

Confounders and Effect Measure Modifiers

To achieve a least biased estimate of association, potential confounders were identified through directed acyclic graph (DAG) analysis. We constructed the DAG based on review of previous literature and knowledge of factors influencing PTB and air pollution. The DAG was analyzed and minimally sufficient adjustment sets were identified using the DAG Program.(Knuppel and Stang 2010) Identified covariates included maternal race, maternal education level, marital status, maternal age at delivery, and ozone. Maternal demographic factors are risk factors of PTB and are representative of socio-economic status, which is influential in where a woman resides. As our exposure metric was derived from residential location, these factors are also related to $PM_{2.5}$. Ozone has been linked to PTB and co-occurs temporally and spatially with $PM_{2.5}$.(Lee et al. 2012; Olsson et al. 2013)

Individual characteristic data was extracted from birth certificates, while ozone data was obtained from CMAQ models and exposure estimated in a similar manner to $PM_{2.5}$. Potential effect measure modifiers (EMM; i.e., factors where the effect of exposure may be different at various levels) identified a priori included race (black, non-black), smoking status (smoker, non-smoker), infant sex (male, female), and maternal parity (primiparous, multiparous). Potential differences in risks due to $PM_{2.5}$ composition by state were also investigated. All EMM variables were extracted from birth certificates.

Statistical analysis

Crude and adjusted risk differences were estimated using single and multi-variable modified Poisson regression with an identity link.(Spiegelman and Hertzmark

2005; Zou 2004) Each category of PTB was used as a dichotomous outcome in separate models. $PM_{2.5}$ was treated as a continuous variable. Individual models were produced for exposure during each week of gestation and each lag. Two sets of adjusted models were created: models adjusted for demographic characteristics and models adjusted for co-occurring ozone. EMM was tested by running models with an interaction term for each potential modifier and continuous $PM_{2.5}$, and performing a -2 log likelihood test. EMM significance was set at $p<0.05$ due to the large population. All analyses were performed using SAS version 9.3 (Cary, NC).

4.4 Results

Of the 1,940,212 eligible pregnancies, a total of 1,781,527 were included in the adjusted analyses (not missing major covariates). Eight percent were classified as preterm. Differences in demographic characteristics of women having term or preterm births were larger with decreasing gestational ages (Table 4.1). Women with preterm pregnancies were less likely to have a bachelor's degree or be married at time of delivery, and were more likely to be black than women with term pregnancies. Distribution of maternal age did not differ across PTB categories.

Table 4.1: Maternal and fetal characteristics across term and preterm birth categories for included pregnancies to women living in OH, PA, or NJ 2000-2005.

	ExPTB[a] (N=8,664)	VPTB[b] (N=12,004)	MPTB[c] (N=31,446)	LPTB[d] (N=90,037)	Term births[e] (N=1,639,376)
			N (%)		
Maternal Education					
Grad school	550 (6)	933 (8)	2,865 (9)	9,245 (10)	202,783 (12)
Bachelor's degree	1,021 (12)	1,651 (14)	4,688 (15)	14,964 (17)	325,596 (20)
Some college	1,905 (22)	2,604 (22)	6,982 (22)	20,429 (23)	372,682 (23)
High School diploma	3,221 (37)	4,227 (35)	10,789 (34)	29,566 (33)	491,888 (30)
Some High School	1,664 (19)	2,199 (18)	5,048 (16)	12,918 (14)	185,703 (11)

<8th grade	303 (3)	390 (3)	1,074 (3)	2,918 (3)	60,724 (4)
Maternal Race/Ethnicity					
Non-Hispanic White	4,120 (48)	6,549 (55)	18,848 (60)	58,868 (65)	1,152,731 (70)
Non-Hispanic Black	3,279 (38)	3,671 (31)	7,781 (25)	17,034 (19)	225,430 (14)
Hispanic	256 (3)	447 (4)	1,382 (4)	4,131 (5)	83,507 (5)
Other	1,009 (12)	1,337 (11)	3,435 (11)	10,004 (11)	177,708 (11)
Maternal Age					
<15	126 (1)	141 (1)	290 (1)	637 (1)	8,033 (<1)
15-19	1,228 (14)	1,408 (12)	3,259 (10)	8,496 (9)	131,159 (8)
20-24	2,114 (24)	2,798 (23)	7,166 (23)	20,201 (22)	352,319 (21)
25-29	2,031 (23)	2,768 (23)	7,582 (24)	23,058 (26)	438,679 (27)
30-34	1,844 (21)	2,821 (24)	7,584 (24)	22,587 (25)	446,350 (27)
35-39	1,044 (12)	1,620 (13)	4,387 (14)	12,070 (13)	218,275 (13)
40-44	259 (3)	423 (4)	1,108 (4)	2,816 (3)	42,739 (3)
45+	18 (<1)	25 (<1)	70 (<1)	172 (<1)	1,822 (<1)
Infant Sex					
Male	4,536 (52)	6,368 (53)	16,781 (53)	48,017 (53)	835,429 (51)
Female	4,124 (48)	5,636 (47)	14,664 (47)	42,019 (47)	803,931 (49)
Missing	4 (<1)	0 (0)	1 (<1)	1 (<1)	16 (<1)
Smoker					
No	6,639 (77)	9,216 (77)	24,446 (78)	72,374 (80)	1,385,050 (84)
Yes	1,893 (22)	2,669 (22)	6,722 (21)	17,028 (19)	245,218 (15)
Missing	132 (2)	119 (1)	278 (1)	635 (1)	9,108 (1)
Marital Status					
Married	3,891 (45)	6,055 (50)	17,481 (56)	55,582 (62)	1,118,053 (68)
Single	4,773 (55)	5,949 (50)	13,965 (44)	34,455 (38)	521,323 (32)
Season of Conception					
Summer	1,977 (23)	2,846 (24)	7,300 (23)	21,054 (23)	387,660 (24)
Fall	2,360 (27)	3,304 (28)	8,763 (28)	24,869 (28)	459,926 (28)
Winter	2,357 (27)	3,224 (27)	8,436 (27)	24,165 (27)	439,416 (27)
Spring	1,970 (23)	2,630 (22)	6,947 (22)	19,949 (22)	352,374 (21)
Parity					
Primiparous	4,343 (50)	5,716 (48)	14,275 (45)	37,605 (42)	655,183 (40)
Multiparous	4,271 (49)	6,225 (52)	17,034 (54)	52,156 (58)	979,929 (60)
Missing	50 (1)	63 (1)	137 (<1)	276 (<1)	4,264 (<1)

a = extremely preterm births (20-27 weeks completed gestation); b= very preterm births (28-31 weeks); c=moderate preterm births (32-34 weeks); d=late preterm births (35-36 weeks); e=term births (37-44 weeks)

Average weekly $PM_{2.5}$ concentrations were similar across categories of PTB for exposures anchored at conception and birth, with means around 14.5μg/m^3 (SD ~5μg/m^3) and interquartile ranges around 6.2μg/m^3 (Table 4.2). Weekly $PM_{2.5}$ concentrations were temporally correlated, with weeks closest to each other having correlation coefficients of approximately 0.4, while correlations for weeks further apart dropped to near 0. Correlation between $PM_{2.5}$ and O_3 concentrations was low, with Pearson correlation coefficients of 0.16 for windows of exposure anchored at conception, and 0.08 for lagged windows of exposure.

Table 4.2: Descriptive statistics for $PM_{2.5}$ (μg/m3) exposure concentrations, averaged over all weeks of exposure

		ExPTB[a]	VPTB[b]	MPTB[c]	LPTB[d]	Term births[e]
Windows of exposure anchored at conception	Minimum	3.73	3.55	3.15	2.84	2.45
	25th Percentile	11.00	10.93	10.87	10.76	10.74
	Median	13.80	13.72	13.65	13.54	13.51
	75th Percentile	17.33	17.24	17.17	17.04	16.98
	Maximum	50.82	50.87	53.33	55.19	58.25
	Mean	14.62	14.54	14.47	14.36	14.31
	Standard Deviation	5.07	5.04	5.03	5.01	4.98
	Inter-Quartile Range	6.33	6.31	6.30	6.28	6.24
Lagged windows of exposure	Minimum	3.71	3.61	2.97	2.95	2.36
	25th Percentile	11.00	10.92	10.88	10.79	10.75
	Median	13.81	13.70	13.68	13.56	13.53
	75th Percentile	17.42	17.24	17.22	17.08	17.04
	Maximum	51.74	48.27	54.46	55.78	59.61
	Mean	14.66	14.53	14.51	14.40	14.35
	Standard Deviation	5.12	5.03	5.07	5.04	5.04
	Inter-Quartile Range	6.42	6.32	6.35	6.29	6.29

a = extremely preterm births (20-27 weeks completed gestation); b= very preterm births (28-31 weeks); c=moderate preterm births (32-34 weeks); d=late preterm births (35-36 weeks) e=term births (37-44 weeks)

In Figure 4.1, an example of the risk differences for all categories of PTB with exposure at gestational week 15 is shown. This figure shows the changes in precision and magnitude for each outcome, demonstrating the need for varied scales across PTB categories.

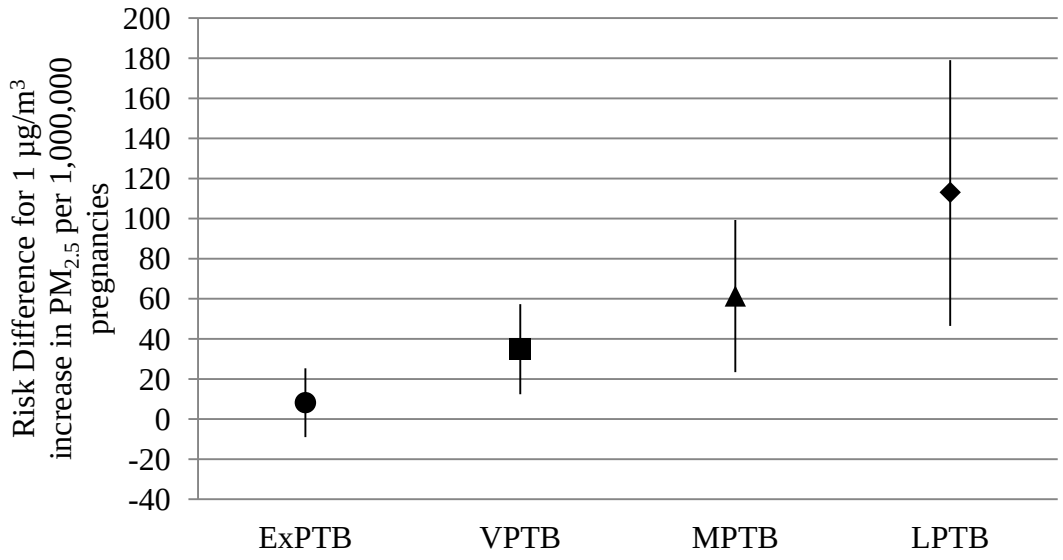


Figure 4.1: An example of risk differences for all categories of preterm birth, exposure at gestational week 15. Risk differences for preterm birth with 1µg/m^3 increases in particulate matter under 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are average concentration of $PM_{2.5}$ for week 15 of gestation. ExPTB = birth at 20-27 weeks of gestation. VPTB = birth at 28-31 weeks of gestation. MPTB = birth at 32-34 weeks of gestation. LPTB = birth at 35-36 weeks of gestation. As outcome gestational age increases so too do magnitudes and confidence limits, indicating need for differing scales for each outcome as seen in subsequent figures.

Results for exposure anchored at conception are presented in Figure 4.2. For extremely preterm birth (Figure 4.2a), elevated risks were seen with exposure to $PM_{2.5}$ in gestational weeks 2-6 and weeks 14-20. The pattern in elevation in risk was more consistent for exposures in early pregnancy weeks. For very preterm birth (Figure 4.2b),

elevations in risk are highest with exposures at gestational weeks 4-9 and with exposures at gestational weeks 15-24. Risks for this category were unusual in that there were two drops in the risk pattern, one in middle pregnancy at weeks 10-14, and one late in pregnancy at weeks 25-28. For moderate preterm birth (Figure 4.2c), risks were elevated with exposure to $PM_{2.5}$ at gestational week 4 and increased with exposure through gestational week 12. Risks dropped at week 13, though remained positive through the rest of pregnancy. For late preterm birth (Figure 4.2d), the elevation in early risk was not seen, with low to null risks with exposures to $PM_{2.5}$ through week 19. After week 20, elevation in risk remained through week 35. While some commonalities are present—e.g., the very and moderate preterm groups in particular were very similar—there were distinct patterns of risk with $PM_{2.5}$ exposure at specific gestational weeks for each category of birth. Estimates were robust to differing covariate adjustment sets.

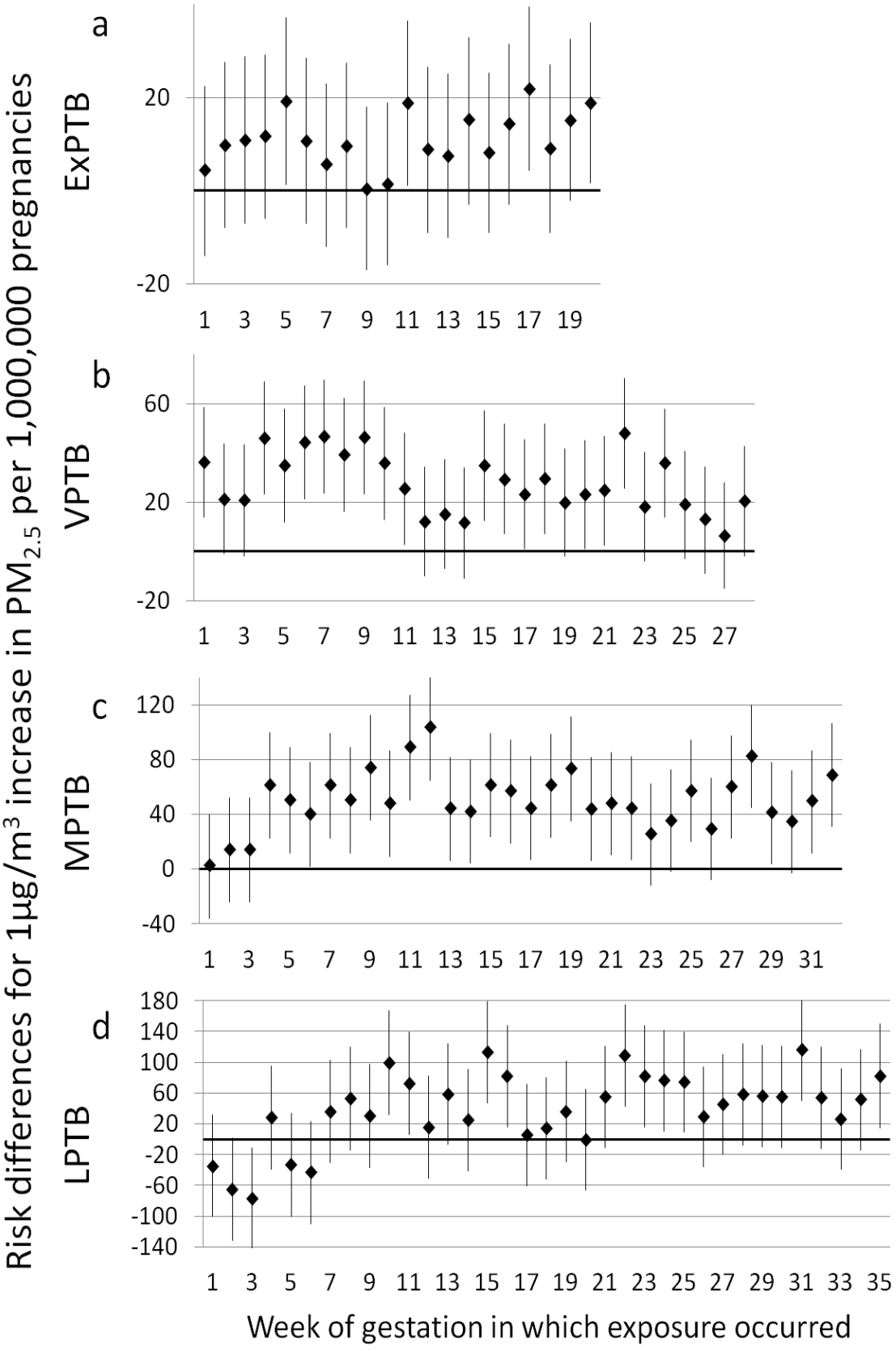

a
ExPTB
20
-20
1 3 5 7 9 11 13 15 17 19
b
VPTB
60
20
-20
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
120
80
40
0
-40
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
180
140
100
60
20
-20
-60
-100
-140
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Risk differences for 1µg/m3 increase in PM2.5 per 1,000,000 pregnancies
Week of gestation in which exposure occurred

Figure 4.2: Results for $PM_{2.5}$, exposures anchored at conception. Risk differences for preterm birth with 1µg/m3 increases in particulate matter under 2.5 micrometers in aerodynamic diameter (PM2.5) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at time of conception. a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB)

Results for exposures lagged from birth are presented in Figure 4.3. Risks were consistently elevated for exposures 0 to 2 weeks from birth across PTB categories, but patterns across PTB categories were not consistent for exposures lagged further from birth. Risk generally dropped to null around lag period 3, then increased again for extreme to moderate PTB but not for late PTB. Estimates were robust to differing adjustment sets.

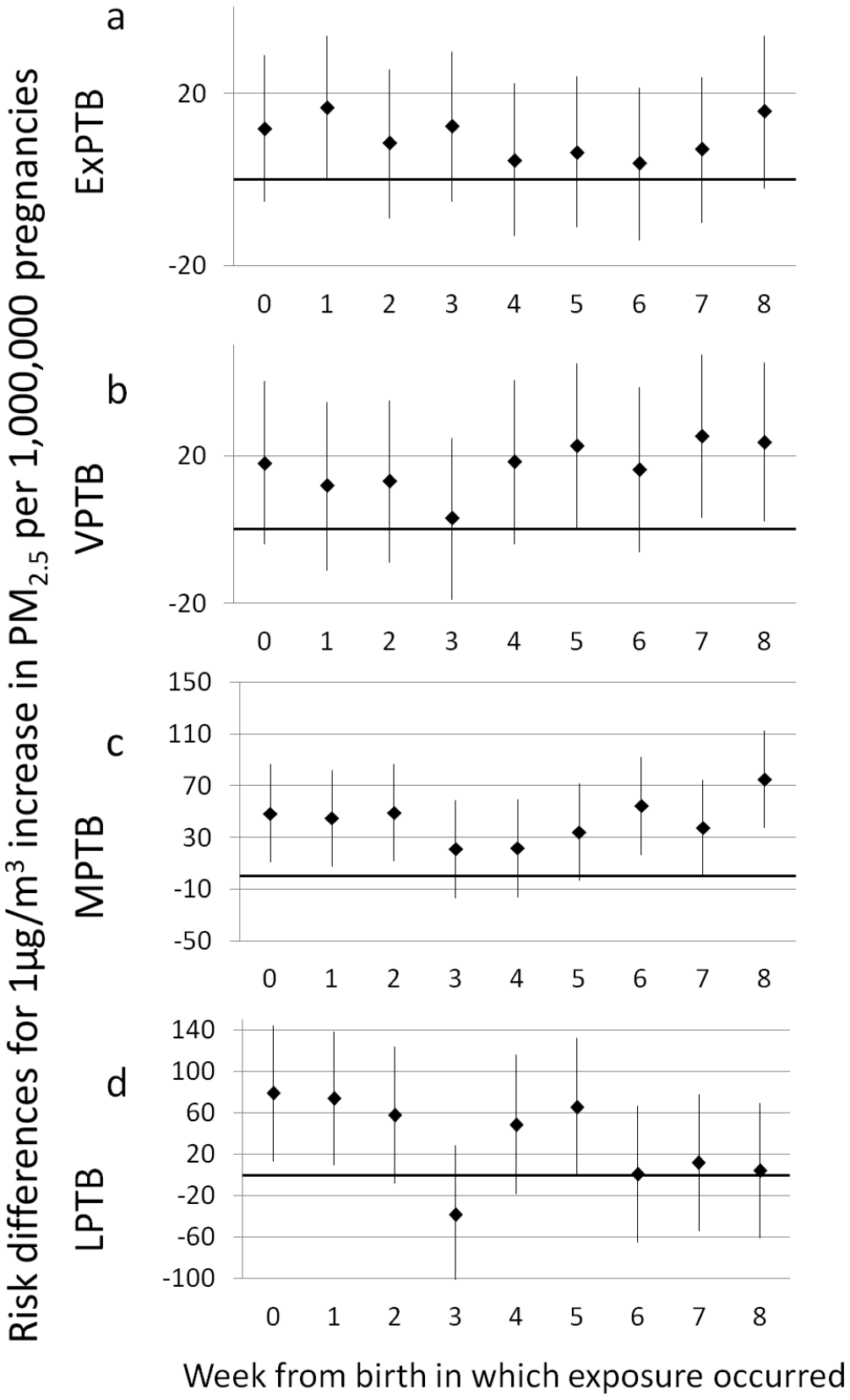

a
ExPTB
20
-20
0 1 2 3 4 5 6 7 8
b
VPTB
20
-20
0 1 2 3 4 5 6 7 8
c
MPTB
150
110
70
30
-10
-50
0 1 2 3 4 5 6 7 8
d
LPTB
140
100
60
20
-20
-60
-100
0 1 2 3 4 5 6 7 8
Risk differences for 1µg/m³ increase in PM2.5 per 1,000,000 pregnancies
Week from birth in which exposure occurred

Figure 4.3: Results for $PM_{2.5}$, lagged exposures. Risk differences for preterm birth with 1µg/m3 increases in particulate matter under 2.5 micrometers in aerodynamic diameter (PM2.5) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at birth. a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB)

No effect measure modification was seen for race (black v. non-black), parity (primiparous - no previous live births v. multiparous - ≥1 previous live births), maternal ever smoking status, or infant sex. No differences in risk were seen by state of birth.

4.5 Discussion

In this study, we examined the associations between exposure to $PM_{2.5}$ at each week of pregnancy and preterm birth categories. We found positive risk differences with $PM_{2.5}$ exposure in early and late gestational weeks and with near-birth exposures. Our findings support the potential for multiple or overlapping pathways of action for $PM_{2.5}$ on preterm birth, based both on timing of exposure and severity of outcome.

Our study results for $PM_{2.5}$ exposures in pregnancy were consistent with several studies focused on various exposure windows. For $PM_{2.5}$ exposures in early pregnancy, five studies across different geographic areas have found positive odds ratios (OR).(Chang et al. 2012; Hansen et al. 2006; Huynh et al. 2006; Jalaludin et al. 2007; Lee et al. 2012; Ritz et al. 2007) Fewer studies have reported positive associations for exposures late in pregnancy or near birth, but among those that have, effects are generally consistent (ORs ~1.05).(Chang et al. 2012; Gehring et al. 2011; Hansen et al. 2006; Wilhelm and Ritz 2005) Effects of $PM_{2.5}$ exposures in middle pregnancy have been less

reported, however Chang et al.(2012) found effects with exposure to $PM_{2.5}$ in both the first and second trimesters. These studies primarily used monitors or monitoring based methods (e.g., kriging, land-use regression) of exposure assessment. While kriging and land use regression provided improvement for some studies by imputing complete spatial and temporal coverage, those methods are best suited for areas with reasonably dense spatial and temporal monitoring (e.g. larger cities). Chang et al.(Chang et al. 2012) examined $PM_{2.5}$ exposure in North Carolina using both monitor data and monitor-corrected CMAQ data, finding similar results for women with exposure information from both sources. For our study, which includes urban, suburban, and rural regions, for which monitor data is not always available, the use of monitor-corrected CMAQ data offers complete spatial and temporal coverage. This coverage expands generalizability of our results as the population is not restricted to urban areas. Our large population, with nearly 1.75 million pregnancies, also allowed examination of effect measure modification by several factors and detection of small effects across multiple time windows of exposure. Like our study, Warren et al.(Warren et al. 2012) evaluated weekly windows of exposure, finding elevated risks with $PM_{2.5}$ exposure in weeks 4-22 of gestation. While this study's results do not perfectly align with our study, possibly due to differences in $PM_{2.5}$ composition in the study areas (Texas, v. northeast states), they do corroborate our findings for exposures in the early weeks of gestation. Our identification of increased risk in specific vulnerable periods in development may aid in the elucidation of potential mechanisms of action.

A handful of studies have reported inverse or null ORs with $PM_{2.5}$ exposure in early pregnancy. Jalaludin et al.(2007) found inverse ORs, though only for exposures

occurring in summer months. Gehring et al.(2011) found inverse associations with $PM_{2.5}$ exposures in the first trimester and last month before birth, though with adjustment for region these effects were attenuated to the null (first trimester) or reversed (last month before birth). This shift in effect with regional adjustment may suggest a role for varied $PM_{2.5}$ composition. Darrow et al.(2009) found null risk ratios for exposures in the first month of gestation and one week before birth. Interestingly both studies which used a more specific definition of preterm birth (27-36 weeks for Chang et al.(2012); 29-36 weeks for Darrow et al.(2009) found opposing results for the first trimester/month of pregnancy. However, this may be due to differences in study design, as Chang et al.(2012) looked at PTB as a time-to-event analysis and Darrow et al employed a time-series approach. Using a cohort study design, our study found mostly positive RDs for these gestational ages and exposure windows, with the exception of LPTBs. Wilhelm et al. found inverse ORs with single pollutant models of $PM_{2.5}$ for exposures early pregnancy in two studies.(Wilhelm and Ritz 2005; Wilhelm et al. 2011) However, in the later study, analysis using multi-pollutant models produced positive ORs for $PM_{2.5}$ exposure.(Wilhelm et al. 2011) This suggests that adjusting for co-occurring pollutants might bring about shifts from inverse or null to positive effect estimates. It is possible that residual confounding due to co-pollutants is also a factor in our study; however, our analyses included co-occurring ozone, and estimates were robust to this inclusion.

Differences in results may happen because of different study populations or because of different research methodologies (exposure assessments, metrics, contrasts, and study designs) across the $PM_{2.5}$/PTB literature, which continue to challenge direct comparison and interpretation of differences across studies. Some differences in results

across studies may be explained by actual differences in $PM_{2.5}$ composition over time and geographical area due to variation in pollutant sources and meteorological conditions.(Bell et al. 2007) Other differences may result from differences in the measurement of exposure and definition of outcomes. Our study not only used monitor-corrected CMAQ data and examined effects with weekly windows of exposure, but also used refined categories of preterm birth and risk difference as the measures of effect. Preterm birth may have differing etiology based on gestational week, as fetal development and vulnerabilities shift rapidly. Using the four categories may reveal differences in effect estimates that may be masked by collapsing all categories of preterm birth into a single outcome. Finally, we used risk differences because these absolute measures of risk are more easily interpretable and can be simply transformed into a number need to harm (NNH = 1/RD), which provides information about how changes to the exposure would be expected to affect public health. Accordingly, it is important to note that while magnitude of effects for extremely preterm birth may be small, this outcome also carries the most severe consequences; therefore even the small changes we observed may impact public health.

Like most studies of air pollution and preterm birth, we have relied on imperfect exposure classification, and the results may reflect residual or unmeasured confounding. Exposure misclassification may be due to the use of a model for exposure assessment (even with bias correction), the use of ambient rather than personal data, the use of a single residential point rather than a profile of where a woman's time is spent, and the assumption that residence at birth was unchanged throughout pregnancy. These factors would likely be nondifferential by outcome, though not necessarily by confounding

factors (e.g., race). Their impact on observed effects may be somewhat complicated. If a woman works in an area with higher pollution or spends a large amount of time commuting, her observed exposure may be lower than her true exposure, thus potentially biasing her observed response toward the null. Or a woman might spend most of her time indoors, information not captured by our data, and her true exposure may be lower than her observed exposure, thus potentially biasing her observed response away from the null.(Allen et al. 2012; Hodas et al. 2012) Unfortunately it is impossible to know what the true exposure conditions are for every woman. In addition, exposure to $PM_{2.5}$ represents exposure to various chemical species that can impact health but are not distinguished in this composite measurement. Thus, the properties of $PM_{2.5}$ that drive these results are unclear. Interpretatively, we focus on the effect of ambient exposures, which are also those most likely to be affected by changes in policy regarding air pollution. Bias due to residual or unmeasured confounding may arise from the use of proxy variables for socio-economic status or the lack of measurement of an important contributing variable. Socio-economic status is not well defined; while the variables we use to approximate SES factors are commonly used in this manner, they may not fully capture the influence of socioeconomic status on the $PM_{2.5}$/PTB association.

In general, the positive effect measures seen throughout the literature indicate that $PM_{2.5}$ is playing a role, though perhaps a complex and subtle one, in the mechanisms of preterm birth. While the mechanisms of $PM_{2.5}$'s actions on preterm birth are not well understood at present, several pathways are possible. Inflammatory processes are a likely pathway of action for $PM_{2.5}$, and inflammation has been linked to $PM_{2.5}$ exposure. $PM_{2.5}$ exposure has been linked to increases in markers of systemic inflammation associated

with preterm delivery, such as high sensitivity C-reactive protein (CRP) and fibrogen.(Backes et al. 2013) Increases in CRP have also been shown with exposures specific to early pregnancy.(Lee et al. 2012) Maternal inflammation may lead to adverse fetal effects, potentially through altered placental vascular function.(Backes et al. 2013) In a study of mice, Veras et al.(Veras et al. 2008) found changes in placental morphology with PM exposure, including decreases in maternal blood space volume and maternal-fetal surface ratio and increased fetal capillary proliferation. These changes may lead to preterm birth through inadequate placental perfusion or impaired nutrient exchange.(Bobak 2000; Kannan et al. 2006) Inflammation may also lead to the creation of reactive oxygen species (ROS), which can cause cell damage, DNA damage, disruption of cellular processes, irreversible protein modifications, or alternations in cellular signaling.(U.S.EPA. 2009)

Our results identify multiple periods of vulnerability to air pollution, depending upon gestational age. The earliest preterm births may be more influenced by infection; exposure to $PM_{2.5}$ may increase susceptibility to infection in these cases rather than having a more direct effect.(Behrman and Butler 2007; U.S.EPA. 2009; Wilhelm and Ritz 2005) Elevated risks of preterm birth with exposure to $PM_{2.5}$ in the early gestational weeks are potentially due to interruption in placental function and implantation.(Veras et al. 2008) Particulates may interfere in placental processes by the transfer of sorbed toxic compounds to the fetus or placenta, inflammatory processes including oxidative stress pathways, or by increasing susceptibility to infectious agents which in turn act on fetal development.(Lee et al. 2012; U.S.EPA. 2009) Increases in preterm birth risk associated with near-birth exposure are possibly the result of nutritional deprivation, wherein the

fetus may produce pro-inflammatory cytokines which can trigger the cascade of events leading to labor and birth.

This study identified the associations between $PM_{2.5}$ exposure at some weeks of gestation and the risk of four categories of preterm birth for women residing in OH, PA, or NJ from 2000 to 2005. $PM_{2.5}$ exposures in early and late gestation were associated with increased risks of preterm birth, though specific critical windows of exposure varied by preterm birth category. Exposures beginning around the time of implantation and near birth appear to be of particular importance. The ubiquitous nature of particulate matter means exposure increases the potential for harm, even when effect magnitudes are small. Many properties of $PM_{2.5}$ could be responsible for the observed effects, and further studies examining specific $PM_{2.5}$ components or properties could add valuable information about the properties of particulate matter for which regulation or intervention should be targeted to reduce adverse outcomes.

This work does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Chapter 5: Exposure to the elemental carbon, organic carbons, nitrate, and sulfate fractions of $PM_{2.5}$ during pregnancy and risk of birth at preterm gestational ages

5.1 Overview

Particulate matter <2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) has been variably associated with preterm birth (PTB), but the roles of $PM_{2.5}$ species have been less studied. We estimated risk of birth in 4 preterm categories (risks reported as PTBs per 10^6 pregnancies) associated with change in ambient concentrations of elemental carbon (EC), organic carbons (OC), nitrates (NO_3), and sulfates (SO_4). From live birth certificates with clinical estimate of gestation and date of delivery, we constructed a cohort of singleton pregnancies with fetus at or beyond 20 weeks of gestation between 2000-2005(n=1,940,213; 8% PTB). We estimated mean species exposures for each week of gestation from monitor-corrected Community Multi-Scale Air Quality modeling data. Risk Differences(RD(95% confidence intervals)) for PTB categories (defined by gestational age of 20-27; 28-31; 32-34; and 35-36) were estimated for each exposure using modified Poisson linear regression adjusted for maternal race, marital status, education, age, and ozone. RD estimates varied by exposure window and outcome period. EC was generally associated with increased risks for births between 28-34 weeks (e.g. a 0.25μg/m^3 increase in EC exposure at gestational week 5 RD=84(-5, 172) and RD=97(-50, 243) for birth at weeks 28-31 and 32-34, respectively). Associations with OCs were generally null or negative. RDs for NO_3 were elevated in the early weeks of gestation and

null in later weeks. RDs for SO_4 exposure were generally positively associated with PTB. EC and SO_4 appear to be influential contributors to $PM_{2.5}$'s role in PTB. Risk of PTB has diverse windows of vulnerability for exposure to species of $PM_{2.5}$.

5.2 Background

Particulate matter under 2.5 aerodynamic micrometers in diameter ($PM_{2.5}$), regulated under the Clean Air Act as a criteria air pollutant, is a complex mixture of extremely small particles and liquid droplets. The chemical composition of $PM_{2.5}$ varies spatially and temporally, as does the strength of associations between PM and various health effects, which may reflect variation in PM toxicity depending on the species/components of PM composition.(Bell et al. 2007; Dutton et al. 2009; Lippmann 2009; Schlesinger et al. 2006) $PM_{2.5}$ exposure has been studied with many health outcomes, among them preterm birth (PTB). Preterm birth is a marker for fetal underdevelopment and a risk factor for further poor health outcomes.(Behrman and Butler 2007; Callaghan et al. 2006; Gilbert et al. 2003; Mathews and MacDorman 2010; Saigal and Doyle 2008)

While most studies of $PM_{2.5}$ and PTB use $PM_{2.5}$ mass as the exposure metric due to limited speciated data, four studies have examined the associations between $PM_{2.5}$ species and PTB.(Brauer et al. 2008; Darrow et al. 2009; Gehring et al. 2011; Wilhelm et al. 2011) These studies have found elevations in risk or odds of preterm birth associated with exposure to elemental carbon (EC), nitrate (NO_3), sulfate (SO_4), and organic carbons (OC). However, null or inverse risks/odds have also been observed for these chemicals depending on study or window of exposure examined. Studies of $PM_{2.5}$ and PTB vary in

design, the species examined, the windows of exposure, and other factors. Multi-pollutant, large-scale exposure assessment has been a challenge to most studies. Two studies that examined a close corollary of EC (black carbon/soot) lacked continuous EC monitoring data for use in land-use regression models; therefore they used PM monitoring data to adjust for temporal fluctuations.(Brauer et al. 2008; Gehring et al. 2011) A time-series by Darrow et al. looked at a number of different species but used a single monitoring location.(Darrow et al. 2009) Because all studies depended on monitoring data, study samples were limited to areas with monitors.

Despite the sparse data on the relationship between $PM_{2.5}$ species and preterm birth, there are some hints that certain species may be more influential than others.(Darrow et al. 2009; Wilhelm et al. 2011) This study builds upon previous research to examine the chemical components of $PM_{2.5}$ in relation to preterm birth by investigating a large study area with a wide range of $PM_{2.5}$ levels and investigating multiple species and exposure periods. We examine the association between ambient EC, OC, SO_4, and NO_3 and risk of PTB using a cohort of fetuses reaching at least 20 weeks gestation across six years in three states. We employ the EPA's Community Multiscale Air Quality (CMAQ) model, which offers complete spatial coverage and daily estimated air pollutant concentrations, leading to a more extensive study area and population. We estimate risk differences for 1μg/m^3 increases in average weekly OC, NO_3, and SO_4 exposures, and 0.25μg/m^3 increases for EC at each week of gestation and birth at four categories of preterm gestation.

5.3 Methods

Study population

Live birth records provided by the State Health Departments of Pennsylvania (PA), New Jersey (NJ), and Ohio (OH) were used to construct a cohort of fetuses reaching at least 20 weeks gestation. This cohort consisted of those fetuses that were at risk of preterm birth for the period between 1 January 2000 and 31 December 2005. From all birth records (n=2,495,350) we restricted the sample to singleton pregnancies with no recorded birth defects, an estimated gestational age available, and having achieved gestational week 20 no earlier than 1 January 2000 and gestational week 45 no later than 31 December 2005, reducing the number of births to 2,142,915 (excluding 352,435). A geocodeable (latitude and longitude assignable) birth address was also required (excluding 202,702). These restrictions lead to an eligible study population of 1,940,213 pregnancies.

Gestational age, pregnancy start, and preterm birth status

Gestational age was determined by clinical estimate of gestation as reported on birth certificates. Start date of pregnancy (aka "time of conception") was calculated by subtracting the clinical estimate of completed gestational weeks from date of birth. Preterm birth status was defined as having a gestational age between 20-36 completed weeks. PTB was further subset into four categories based on World Health Organization definitions and consideration of the literature: extremely PTB (ExPTB) gestational age between 20-27 weeks; very PTB (VPTB) gestational age between 28-31 weeks; moderate PTB (MPTB) gestational age between 32-34 weeks; and late PTB (LPTB) gestational age

of 35-36 weeks. Term births were births between 37-45 completed gestational weeks. These categorizations were made to better elucidate the severity of health response and the potential for variety of response to exposure based on gestational age, as development occurs rapidly during this period and the full range of PTB covers 4 months of gestation, and during the different developmental stages the growing fetus may be differently vulnerable to insult.

Exposure data

Maternal address data were taken from all birth records and processed with the ZP4 address locator program (Semaphore Corporation, Monterey, CA) to assign latitude and longitude values to the address based on TIGER street segments (n=2,042,425). Those addresses that did not receive latitude and longitude values (n=452,925) were instead geocoded using the ArcGIS online geocoding service in ArcMap 10 (ESRI, Redlands, CA), which returns a matching location, a tied location, or unmatched status. 197,125 addresses returned as matched; 8949 addresses returned as tied and were hand match to the best candidate. This process resulted in 2,248,499 pregnancies having latitude and longitude values. This data was then merged with outcome and covariate data (as above) for the final study population.

Daily estimated concentrations of $PM_{2.5}$ species (EC, OC, NO_3, SO_4) were provided by the EPA's Atmospheric Exposure Integration Branch for 1999 to 2005 in 12 km grids. These estimates were constructed using output from the Community Multiscale Air Quality model (CMAQ) bias-corrected with monitoring network data, as detailed in Hogrefe et al.(Hogrefe et al. 2009) Briefly, meteorological conditions and criteria

pollutant emissions are input into CMAQ, which simulates chemical and physical processes and chemical transport occurring in the atmosphere, then estimates gridded concentrations of ambient air pollutants.(Byun and Schere 2006; Hogrefe et al. 2009) Baseline concentrations of $PM_{2.5}$ were created by matching grids to monitoring sites and applying a Kolmogorov–Zurbenko (15,5) moving average filter. Adjustment factors for each grid were then created as the ratio of observed to modeled concentrations, spatially interpolated across the gridded field.(Hogrefe et al. 2009) CMAQ output for each grid was then multiplied by its adjustment factor to produce the final bias-corrected estimates.

Daily values for pollutant exposure were assigned to pregnancies by matching geocoded maternal residential location to CMAQ grid. Dates for each day from the calculated start of pregnancy to birth were matched to date of CMAQ concentration estimation. Exposure was assigned in two ways. First, we assigned exposure anchored from the "time of conception". $PM_{2.5}$ species concentrations were averaged over fixed seven day periods of gestation to estimate weekly average concentrations (i.e., average of days 1-7 equals concentration for week 1, average of days 2-14 equals concentration for week 2, etc.) for all pregnancies. Second, we assigned exposure windows anchored from date of birth. We lagged fixed windows of 7–day exposures from birth and assigned average $PM_{2.5}$ species concentrations for that week. The lag refers to time from birth; all exposures are a one-week average concentration (non-cumulative). For example, for a birth occurring at week 32, a 2 week lagged exposure would reflect exposure for gestational week 30. While for a birth occurring at week 44, a 2 week lagged exposure would reflect exposure for gestational week 42. Average weekly species concentrations anchored at birth were assigned for lags up to 8 weeks from birth.

Confounders and Effect Measure Modifiers

Potential confounders were identified through directed acyclic graph (DAG) analysis. The DAG was constructed based on previous literature and knowledge of factors influencing preterm birth and air pollution. The DAG was analyzed using The DAG Program (http://epi.dife.de/dag) and minimally sufficient adjustment sets were identified.(Knuppel and Stang 2010) Identified covariates included maternal race, maternal education level, marital status, maternal age at delivery, and ozone. Individual characteristic data was extracted from birth certificates, while ozone data was from CMAQ models and exposure estimated in a similar manner to $PM_{2.5}$ species. Potential effect measure modifiers (EMM) identified a priori included race (black, non-black), smoking status (smoker, non-smoker), infant sex (male, female), and maternal parity (primiparous, multiparous). Except for ozone, all co-variables were extracted from birth certificates. When EMM was observed both marginal and stratified effects are presented, as marginal effects effectively standardized to population distributions reflect the overall impact of exposure to $PM_{2.5}$ species, while stratified effects highlight potentially vulnerable subgroups for more targeted intervention.

Statistical analysis

Crude and adjusted risk differences were estimated using single and multi-variable modified Poisson regression with an identity link.(Spiegelman and Hertzmark 2005; Zou 2004) Each category of PTB was used as a dichotomous outcome in separate models. $PM_{2.5}$ species were treated as continuous variables. Individual models were

performed for each week of exposure anchored at birth and each week of lagged exposure. Three sets of adjusted models were created: those adjusted for demographic characteristics; those adjusted demographic characteristics and co-occurring ozone; and those also adjusting for all $PM_{2.5}$ species. EMM was tested by running models with an interaction term for each potential modifier and continuous species concentration. EMM significance was set at $p<0.05$ due to the large population. All statistical analyses were performed using SAS version 9.3 (Cary, NC).

This research was approved by the University of North Carolina at Chapel Hill's Office of Human Research Ethics (Study # 11-1089), the Pennsylvania Department of Health Bureau of Health Statistics & Research (# 1C-2460), New Jersey Department of Health and Senior Services Institutional Review Board (#0379), and the Ohio Department of Health Human Subjects Institutional Review Board (# 2011-16).

5.4 Results

A total of 1,781,527 pregnancies (out of a potential 1,940,212) were included in the adjusted analysis as they had complete covariate information. Of these, 142,151 (8%) were preterm births. Women with preterm pregnancies, compared to term pregnancies, had lower educational attainment, were more often unmarried, and were more likely to be black (Table 5.1).

Table 5.1: Maternal and fetal characteristics across term and preterm birth categories for eligible pregnancies to women living in OH, PA, or NJ 2000-2005

	ExPTB[a] (N=8,664)	VPTB[b] (N=12,004)	MPTB[c] (N=31,446)	LPTB[d] (N=90,037)	Term births (N=1,639,376)
	N (%)				
Maternal Education					
Grad school	550 (6)	933 (8)	2,865 (9)	9,245 (10)	202,783 (12)

Bachelor's degree	1,021 (12)	1,651 (14)	4,688 (15)	14,964 (17)	325,596 (20)
Some college	1,905 (22)	2,604 (22)	6,982 (22)	20,429 (23)	372,682 (23)
High School diploma	3,221 (37)	4,227 (35)	10,789 (34)	29,566 (33)	491,888 (30)
Some High School	1,664 (19)	2,199 (18)	5,048 (16)	12,918 (14)	185,703 (11)
<8th grade	303 (3)	390 (3)	1,074 (3)	2,918 (3)	60,724 (4)
Maternal Race/Ethnicity					
Non-Hispanic White	4,120 (48)	6,549 (55)	18,848 (60)	58,868 (65)	1,152,731 (70)
Non-Hispanic Black	3,279 (38)	3,671 (31)	7,781 (25)	17,034 (19)	225,430 (14)
Hispanic	256 (3)	447 (4)	1,382 (4)	4,131 (5)	83,507 (5)
Other	1,009 (12)	1,337 (11)	3,435 (11)	10,004 (11)	177,708 (11)
Maternal Age					
<15	126 (1)	141 (1)	290 (1)	637 (1)	8,033 (<1)
15-19	1,228 (14)	1,408 (12)	3,259 (10)	8,496 (9)	131,159 (8)
20-24	2,114 (24)	2,798 (23)	7,166 (23)	20,201 (22)	352,319 (21)
25-29	2,031 (23)	2,768 (23)	7,582 (24)	23,058 (26)	438,679 (27)
30-34	1,844 (21)	2,821 (24)	7,584 (24)	22,587 (25)	446,350 (27)
35-39	1,044 (12)	1,620 (13)	4,387 (14)	12,070 (13)	218,275 (13)
40-44	259 (3)	423 (4)	1,108 (4)	2,816 (3)	42,739 (3)
45+	18 (<1)	25 (<1)	70 (<1)	172 (<1)	1,822 (<1)
Marital Status					
Married	3,891 (45)	6,055 (50)	17,481 (56)	55,582 (62)	1,118,053 (68)
Single	4,773 (55)	5,949 (50)	13,965 (44)	34,455 (38)	521,323 (32)
Smoker					
No	6,639 (77)	9,216 (77)	24,446 (78)	72,374 (80)	1,385,050 (84)
Yes	1,893 (22)	2,669 (22)	6,722 (21)	17,028 (19)	245,218 (15)
Missing	132 (2)	119 (1)	278 (1)	635 (1)	9,108 (1)
Infant Sex					
Male	4,536 (52)	6,368 (53)	16,781 (53)	48,017 (53)	835,429 (51)
Female	4,124 (48)	5,636 (47)	14,664 (47)	42,019 (47)	803,931 (49)
Missing	4 (<1)	0 (0)	1 (<1)	1 (<1)	16 (<1)
Parity					
Primiparous	4,343 (50)	5,716 (48)	14,275 (45)	37,605 (42)	655,183 (40)
Multiparous	4,271 (49)	6,225 (52)	17,034 (54)	52,156 (58)	979,929 (60)
Missing	50 (1)	63 (1)	137 (<1)	276 (<1)	4,264 (<1)

a = extremely preterm births (20-27 weeks completed gestation); b= very preterm births (28-31 weeks); c=moderate preterm births (32-34 weeks); d=late preterm births (35-36 weeks)

Average weekly pollutant concentrations were similar across categories of PTB for windows of exposure anchored at conception and birth; though slightly higher in earlier PTB categories for EC, OC, and NO_3, and slightly lower for earlier PTB categories for SO_4 (Table 5.2). Species concentrations were temporally auto-correlated, though the extent varies by species. Temporal correlation coefficients ranged from: 0.76 to 0.50 for EC; 0.75 to 0 for OC; 0.70 to -0.45 for NO_3; and 0.64 to -0.45 for SO_4. Correlations between species were high for EC-OC (Pearson correlation coefficient ~0.80) and OC-NO_3 (~0.59) and moderate for EC-NO_3 (~0.38), OC-SO_4 (~ -0.21), and NO_3-SO_4 (~ -0.43). EC and SO_4 were not correlated (~ -0.07).

Table 5.2: Descriptive statistics for particulate matter species ($\mu g/m^3$) exposure concentrations, averaged over all weeks of exposure

		Elemental Carbon					Organic Carbon				
		ExPTB	VPTB	MPTB	LPTB	Term	ExPTB	VPTB	MPTB	LPTB	Term
Windows of exposure anchored at conception	Min	0.07	0.06	0.04	0.04	0.02	0.2	0.17	0.12	0.1	0.06
	25th	0.37	0.37	0.36	0.35	0.35	1.12	1.11	1.09	1.07	1.06
	50th	0.51	0.51	0.49	0.48	0.47	1.61	1.59	1.56	1.52	1.51
	75th	0.72	0.71	0.69	0.67	0.65	2.33	2.31	2.26	2.2	2.18
	Max	4.08	4.09	4.39	4.72	5.04	11.65	11.69	12.49	12.85	12.61
	Avg	0.61	0.6	0.58	0.56	0.55	1.9	1.88	1.83	1.79	1.77
	SD	0.37	0.36	0.35	0.34	0.32	1.14	1.12	1.1	1.07	1.05
	IQR	0.34	0.34	0.33	0.32	0.31	1.2	1.22	1.22	1.21	1.09
Windows of exposure lagged from birth	Min	0.06	0.06	0.04	0.04	0.02	0.18	0.16	0.11	0.11	0.05
	25th	0.37	0.36	0.35	0.34	0.34	1.1	1.08	1.06	1.04	1.03
	50th	0.5	0.5	0.48	0.47	0.46	1.57	1.53	1.5	1.46	1.45
	75th	0.71	0.69	0.67	0.65	0.64	2.29	2.23	2.16	2.1	2.08
	Max	4.07	4.14	4.5	4.78	4.99	11.25	12.04	12.63	12.99	13.25
	Avg	0.6	0.59	0.57	0.55	0.54	1.87	1.82	1.77	1.72	1.7
	SD	0.37	0.36	0.34	0.33	0.32	1.14	1.1	1.06	1.03	1.01
	IQR	0.34	0.33	0.32	0.31	0.3	1.18	1.14	1.1	1.06	1.05
		Nitrate					Sulfate				

		ExPTB	VPTB	MPTB	LPTB	Term	ExPTB	VPTB	MPTB	LPTB	Term
Windows of exposure anchored at conception	Min	<0.01	<0.01	<0.01	<0.01	<0.01	0.9	0.9	0.84	0.8	0.69
	25th	0.47	0.47	0.47	0.46	0.45	2.81	2.79	2.79	2.77	2.78
	50th	1.43	1.43	1.4	1.39	1.36	4.48	4.46	4.51	4.51	4.54
	75th	2.75	2.73	2.68	2.65	2.63	7.7	7.66	7.76	7.78	7.82
	Max	11.91	11.95	12.48	12.98	13.38	32.95	33.89	35.51	37.28	41.38
	Avg	1.81	1.8	1.77	1.75	1.74	5.74	5.72	5.77	5.77	5.78
	SD	1.58	1.57	1.55	1.54	1.53	3.95	3.95	3.99	4	3.98
	IQR	2.28	2.26	2.22	2.19	2.18	4.75	4.78	4.91	4.98	4.93
Windows of exposure lagged from birth	Min	<0.01	<0.01	<0.01	<0.01	<0.01	1.11	1.11	1.04	1.01	0.8
	25th	0.44	0.43	0.39	0.39	0.38	2.84	2.85	2.88	2.86	2.86
	50th	1.39	1.34	1.26	1.23	1.19	4.58	4.65	4.79	4.82	4.85
	75th	2.71	2.64	2.54	2.51	2.47	7.88	7.93	8.18	8.23	8.28
	Max	11.85	11.85	12.35	12.89	13.47	32.52	34	36.61	38.19	42.34
	Avg	1.78	1.73	1.67	1.64	1.62	6.03	6.06	6.21	6.23	6.25
	SD	1.58	1.55	1.53	1.5	1.5	4.01	3.98	4.1	4.11	4.12
	IQR	2.26	2.21	2.15	2.12	2.1	5.04	5.08	5.3	5.37	5.41

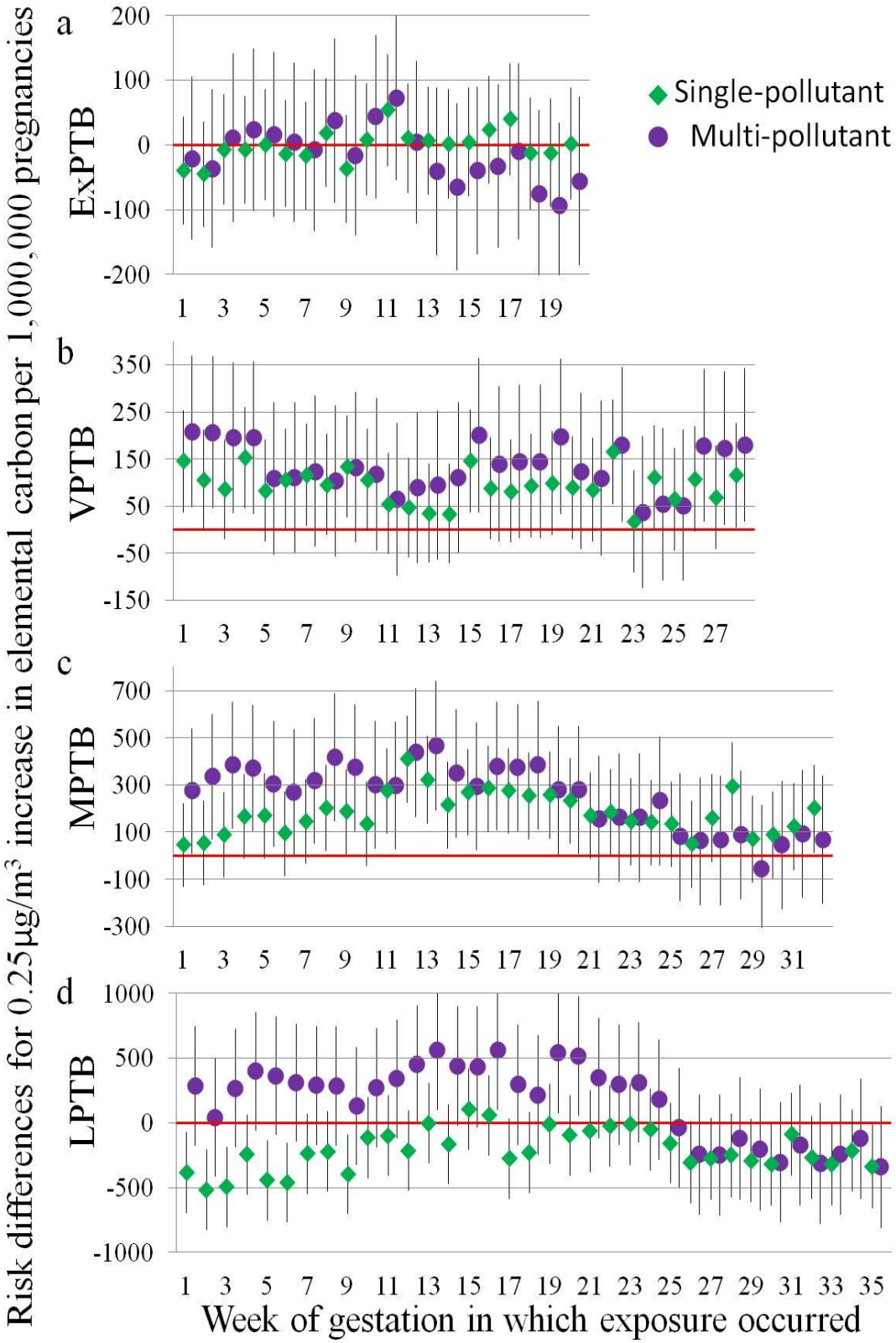
ExPTB = births at 20-27 weeks of gestation; VPTB = births at 28-31 weeks of gestation; MPTB = births at 32-34 weeks of gestation; LPTB = births at 35-36 weeks of gestation; term = births at 37-44 weeks of gestation; SD = standard deviation; IQR = interquartile range

Exposures anchored at conception

Preterm birth risk differences associated with a 0.25μg/m^3 increase in elemental carbon, with exposure anchored at conception, are shown in Figure 5.1. For EC exposure, not adjusted for other $PM_{2.5}$ species, ExPTB risks were null across all gestational weeks (Figure 5.1a). For VPTB (Figure 5.1b), risks were generally positive, though exposures during gestational weeks 11-14 appear near null. For MPTB (Figure 5.1c), risks were elevated with exposure to EC at gestational week 4 and increase with exposure through gestational week 12 and then decrease through week 25. For LPTB (Figure 5.1d), risks were negative in early and later gestational weeks (1-9, 25-35) and null with exposure to

EC in the middle gestational weeks. For multi-pollutant models with all species as covariates, risks associated with EC were similar to single pollutant models for ExPTB and VPTB outcomes. For MPTB, risks for exposures in weeks 1-10 were higher in the multi-pollutant models. This is also true for LPTB; in weeks 1 to 24, RDs were higher for multi-pollutant models and often show a reversal of effect from single pollutant models.

Preterm birth risk differences for single-pollutant models of EC were null for ExPTB and LPTB (Figure 5.1e and 5.1h, respectively) and generally elevated for VPTB and MPTB across lagged windows of exposure (Figure 5.1f and 5.1g). Multi-pollutant models show generally similar results, though effects seem more exaggerated than in single-pollutant models (i.e., positive/negative risks were larger and null risks were closer to 0). Results for ExPTB after lag 4 are not shown as the models were non-convergent.


a
ExPTB
200
100
0
-100
-200
1 3 5 7 9 11 13 15 17 19
Single-pollutant
Multi-pollutant
b
VPTB
350
250
150
50
-50
-150
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
700
500
300
100
-100
-300
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
1000
500
0
-500
-1000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred
Risk differences for 0.25µg/m3 increase in elemental carbon per 1,000,000 pregnancies

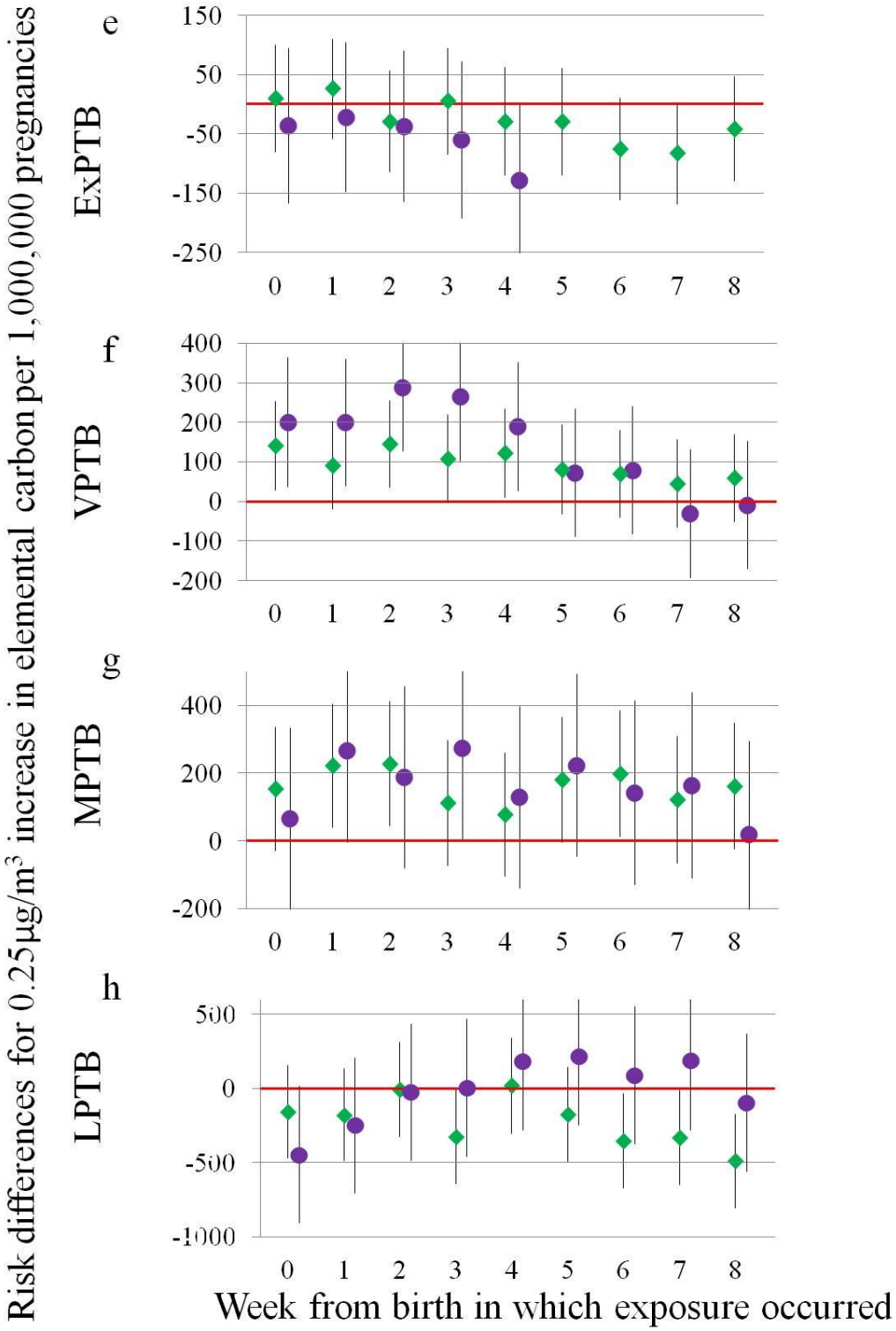
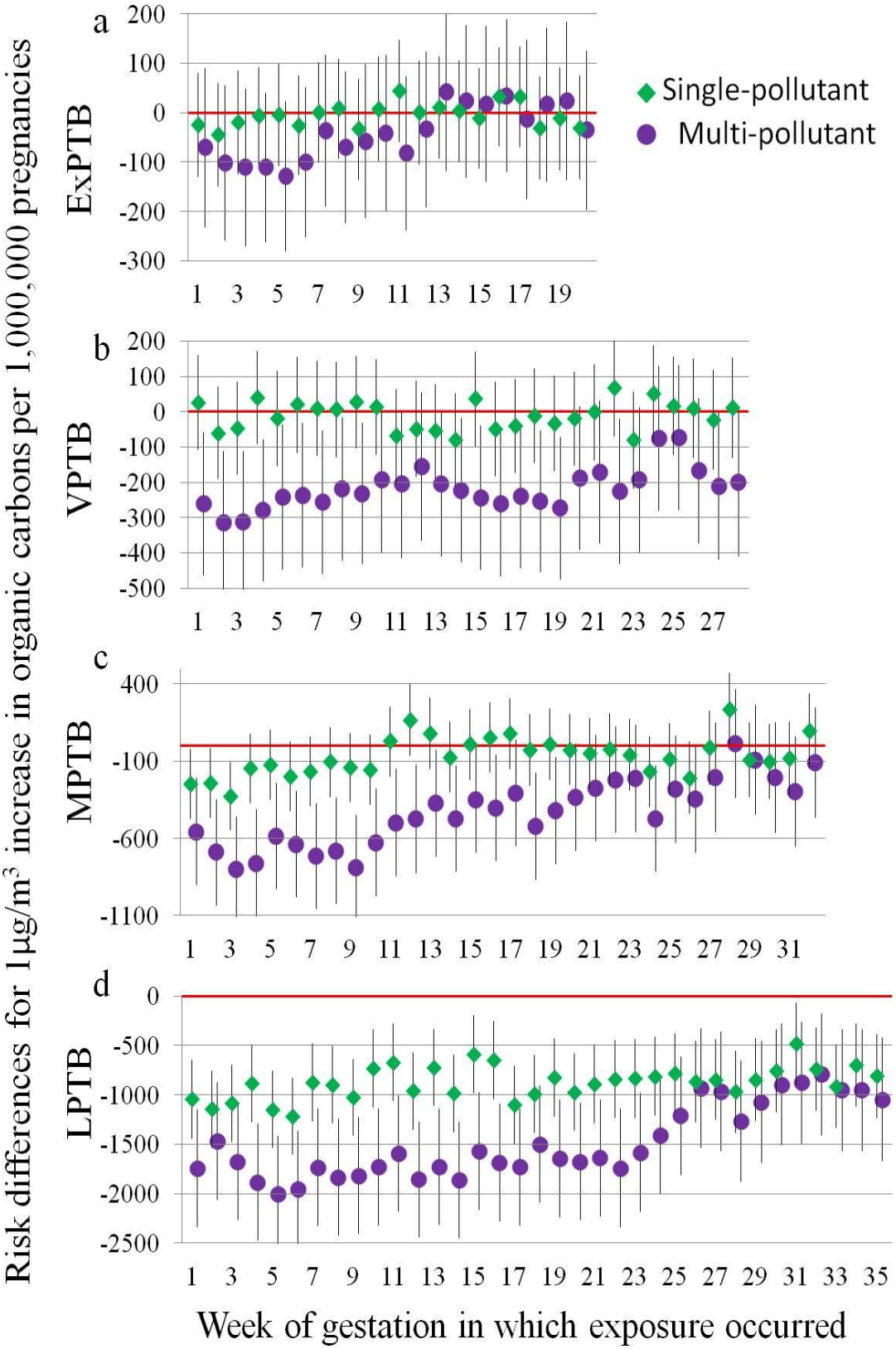

Risk differences for 0.25μg/m³ increase in elemental carbon per 1,000,000 pregnancies
e
ExPTB
150
50
-50
-150
-250
0 1 2 3 4 5 6 7 8
f
VPTB
400
300
200
100
0
-100
-200
0 1 2 3 4 5 6 7 8
g
MPTB
400
200
0
-200
0 1 2 3 4 5 6 7 8
h
LPTB
500
0
-500
-1000
0 1 2 3 4 5 6 7 8
Week from birth in which exposure occurred

Figure 5.1: Results for elemental carbon, exposures anchored at conception (top) and lagged from birth (bottom). Risk differences for 0.25 µg/m3 increases in elemental carbon per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. "Single-pollutant" models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. "Multi-pollutant" models adjusted for previous factors and co-occurring organic carbons, nitrates, and sulfates. Exposures are anchored at time of conception (left panel) or time of birth and lagged (right panel). Outcomes are as follows: (a & e) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b & f) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c & g) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d & h) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

Preterm birth risk differences for a $1\mu g/m^3$ increase in organic carbons with exposures anchored at conception are shown in Figure 5.2. In single-pollutant models the effects of OC were generally null for ExPTB, VPTB, and MPTB (Figure 5.2a-c). For LPTB, risks were inverse for exposures across all weeks of gestation (Figure 5.2d). In multi-pollutant models, risks remain null for ExPTB but were inverse for VPTB and for exposures in weeks 1-27 for MPTB. For LPTB, risks were lower (more negative) than in single-pollutant models for exposures at weeks 1-25, after which risks were similar to those observed in single-pollutant models.

Preterm birth risk differences for single-pollutant models of OC were elevated with lagged exposures for ExPTB and VPTB (Figure 5.2e and 5.2f). MPTB has a less steady pattern of risk, with elevated risks at lags of 0-2 and 5-8 but null effects for lags 3-4 (Figure 5.2g). For LPTB, risks were null for lags 0-4 then steadily decrease to lag 8 (Figure 5.2h). Risks were generally similar for single- and multi-pollutant models with ExPTB and LPTB. For VPTB, risks in multi-pollutant models were inverse with exposures at 1-3 lagged weeks and null otherwise. For MPTB, risks were generally null.


a
ExPTB
200
100
0
-100
-200
-300
1 3 5 7 9 11 13 15 17 19
Single-pollutant
Multi-pollutant
b
VPTB
200
100
0
-100
-200
-300
-400
-500
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
400
-100
-600
-1100
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
0
-500
-1000
-1500
-2000
-2500
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Risk differences for 1μg/m³ increase in organic carbons per 1,000,000 pregnancies
Week of gestation in which exposure occurred

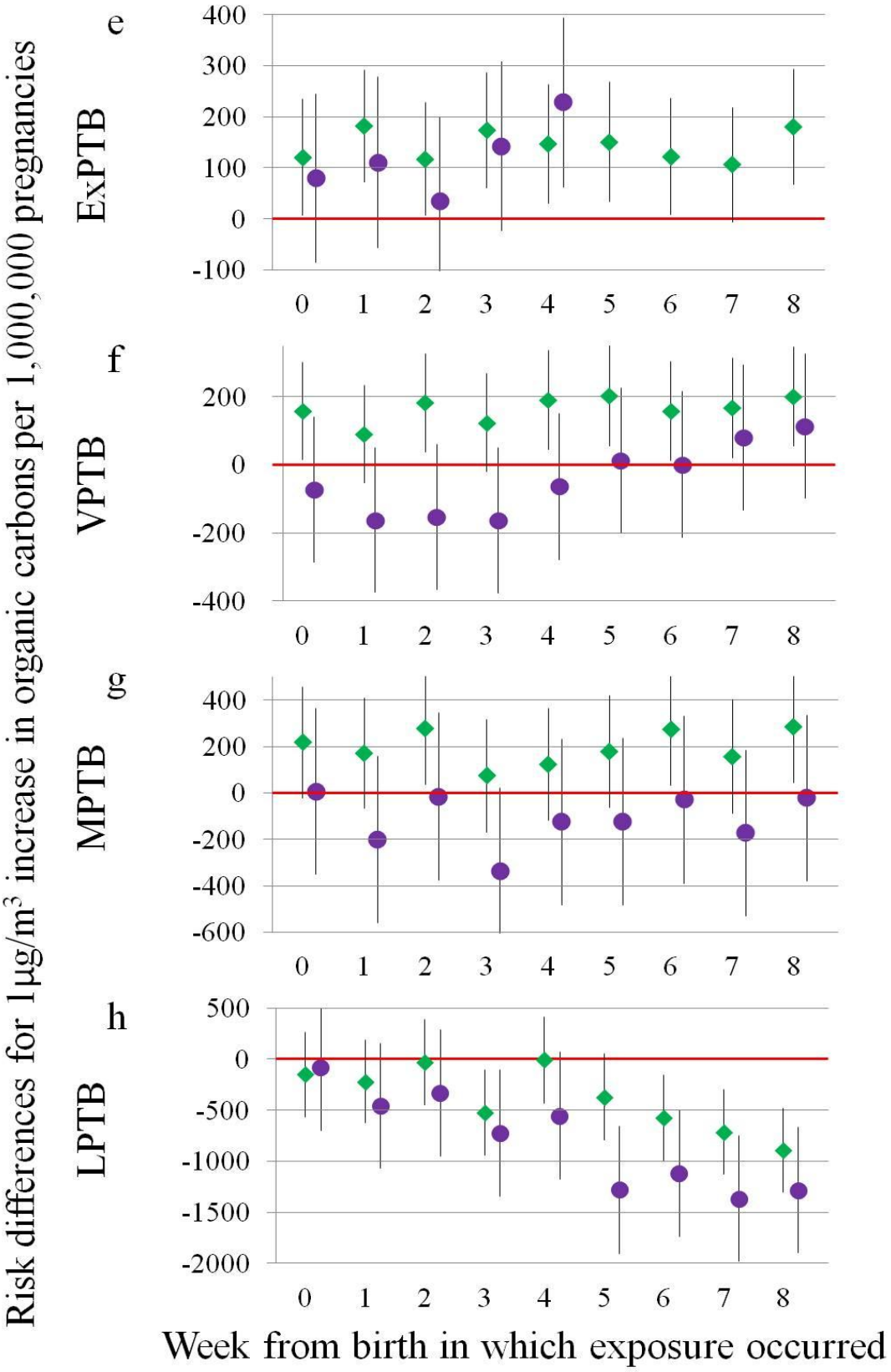
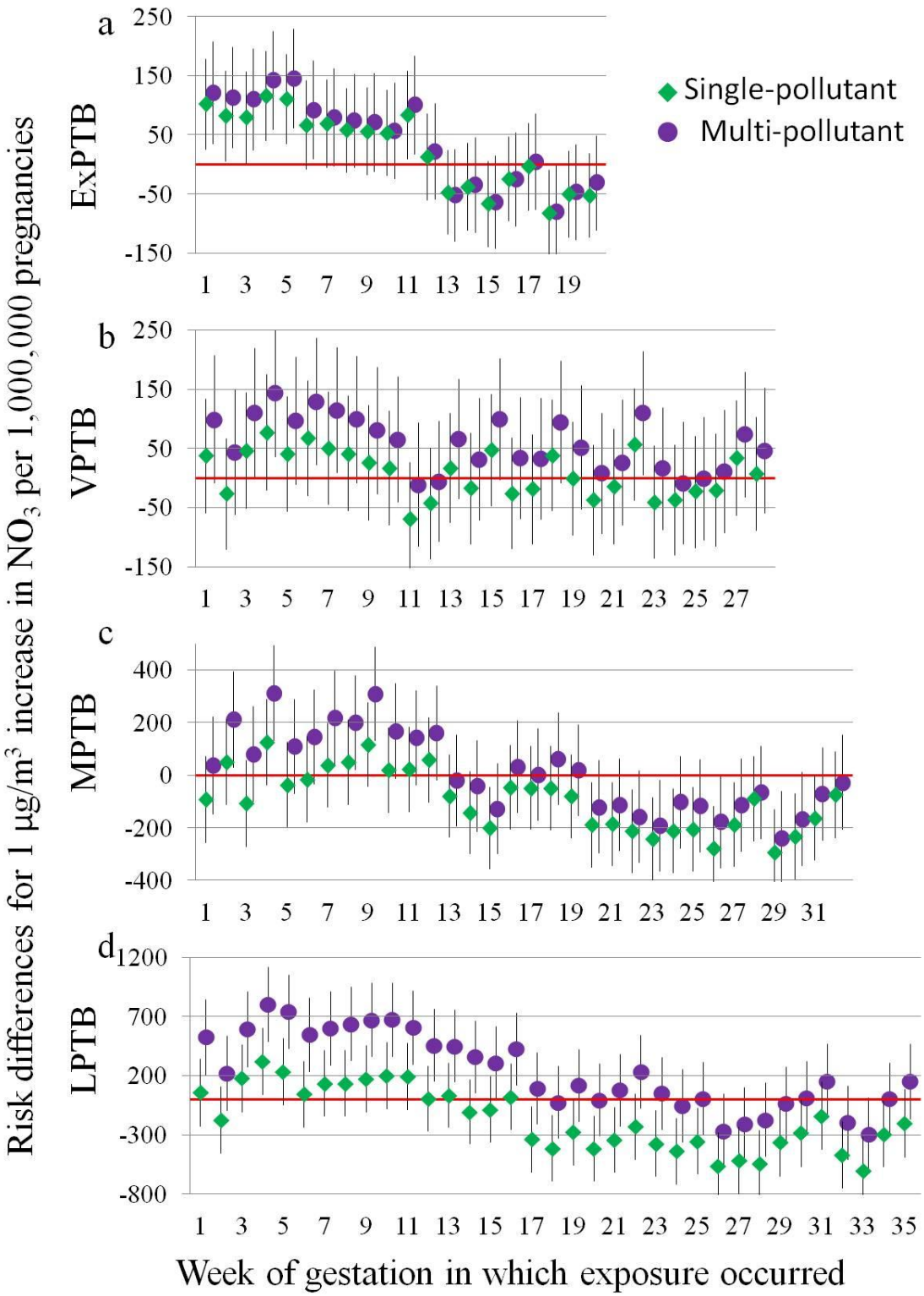

e
ExPTB
400
300
200
100
0
-100
0 1 2 3 4 5 6 7 8
f
VPTB
200
0
-200
-400
0 1 2 3 4 5 6 7 8
g
MPTB
400
200
0
-200
-400
-600
0 1 2 3 4 5 6 7 8
h
LPTB
500
0
-500
-1000
-1500
-2000
0 1 2 3 4 5 6 7 8
Risk differences for 1μg/m3 increase in organic carbons per 1,000,000 pregnancies
Week from birth in which exposure occurred

Figure 5.2: Results for organic carbons, exposures anchored at conception (top) and lagged from birth (bottom). Risk differences for 1 µg/m3 increases in organic carbons per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. "Single-pollutant" models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. "Multi-pollutant" models adjusted for previous factors and co-occurring elemental carbons, nitrates, and sulfates. Exposures are anchored at time of conception (left panel) or time of birth and lagged (right panel). Outcomes are as follows: (a & e) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b & f) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c & g) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d & h) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

Preterm birth risk differences for a $1\mu g/m^3$ increase in NO_3 with exposures anchored at conception are shown in Figure 5.3. For NO_3 exposure, not adjusted for other $PM_{2.5}$ species, risks for ExPTB were elevated at gestational weeks 1-11 then fall to null (Figure 5.3a). For VPTB, risks were slightly elevated at weeks 3-8 and generally null otherwise (Figure 5.3b). For MPTB, risks were generally null in the earlier weeks of gestation, becoming inverse after week 20 (Figure 5.3c). For LPTB, risks were generally null to week 16 and generally inverse in weeks 17-35 (Figure 5.3d). With multi-pollutant models, risks for NO_3 tend to be more positive than those seen in single-pollutant models; for exposures in the earlier weeks of gestation for VPTB, MPTB, and LPTB risks become generally. In other circumstances risks were similar between single- and multi-pollutant models, as in the case of ExPTB.

For NO_3 exposures lagged from birth, preterm risk differences were generally the same between single- and multi-pollutant models and elevated across most lags and categories of PTB (Figure 5.3e-h), though the pattern of elevated risks is not consistent across PTB categories.


a
ExPTB
250
150
50
-50
-150
1 3 5 7 9 11 13 15 17 19
Single-pollutant
Multi-pollutant
b
VPTB
250
150
50
-50
-150
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
400
200
0
-200
-400
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
1200
700
200
-300
-800
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Risk differences for 1 μg/m³ increase in NO3 per 1,000,000 pregnancies
Week of gestation in which exposure occurred

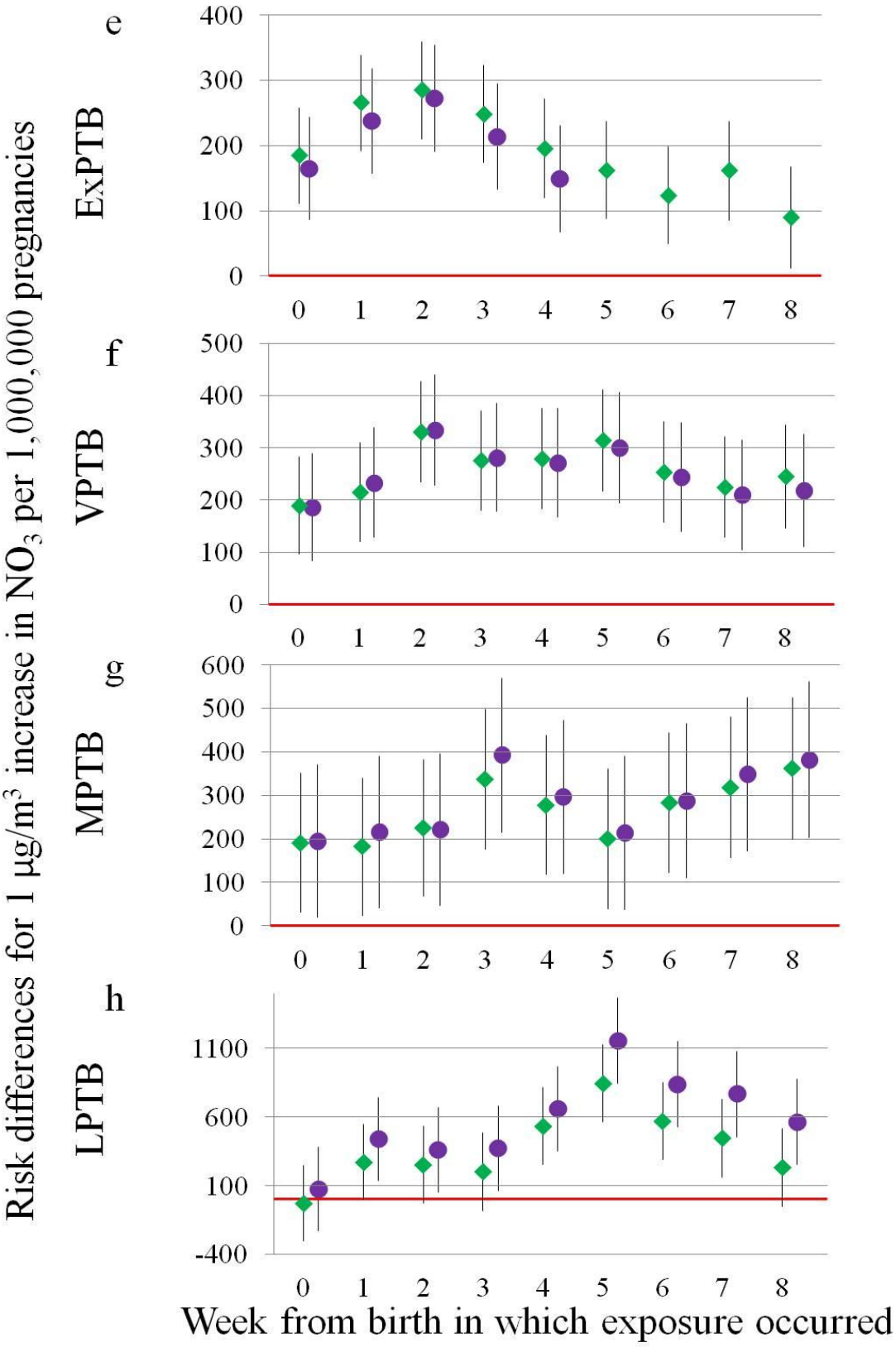
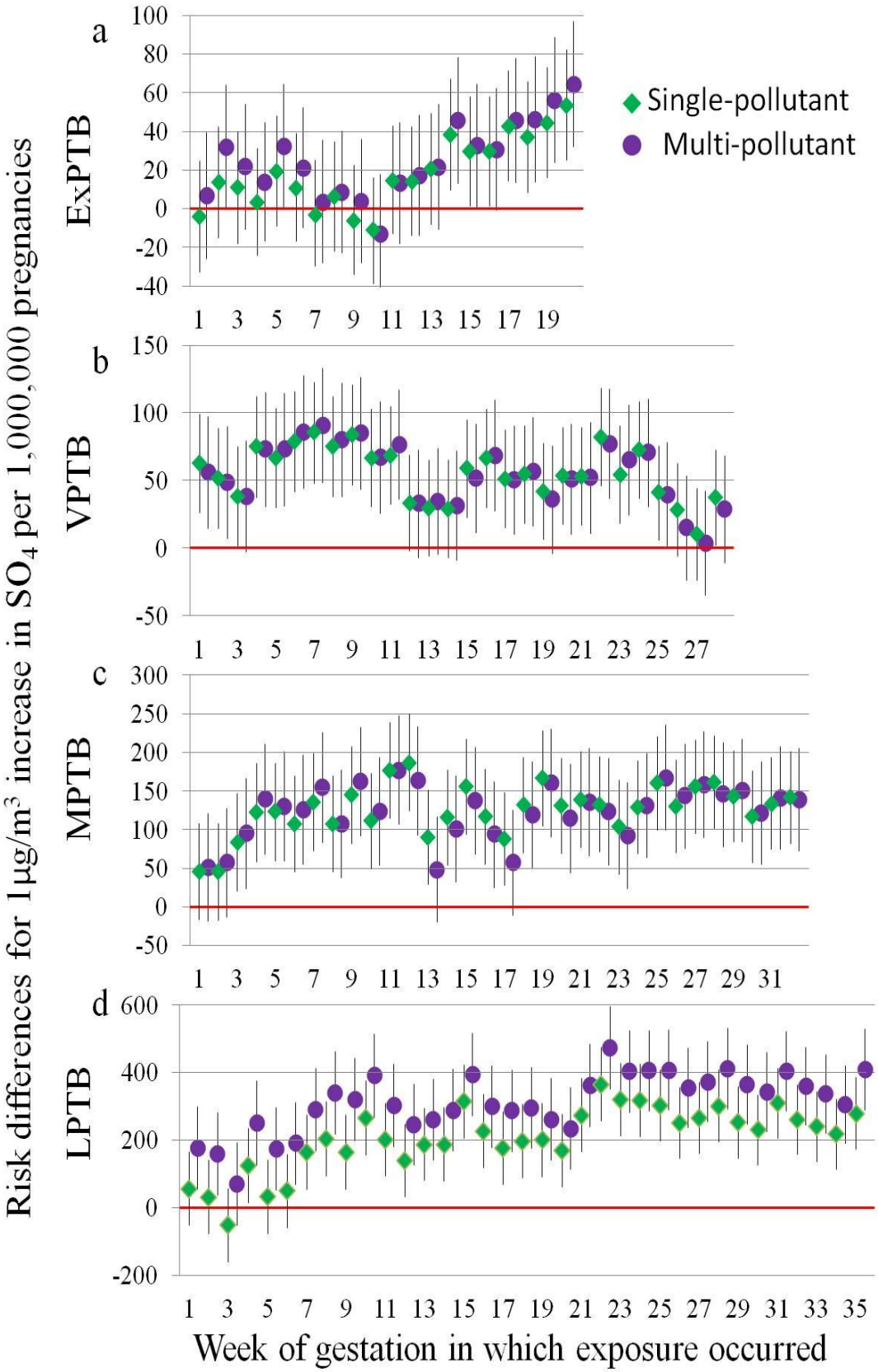

e
ExPTB
400
300
200
100
0
0 1 2 3 4 5 6 7 8
f
VPTB
500
400
300
200
100
0
0 1 2 3 4 5 6 7 8
g
MPTB
600
500
400
300
200
100
0
0 1 2 3 4 5 6 7 8
h
LPTB
1100
600
100
-400
0 1 2 3 4 5 6 7 8
Risk differences for 1 μg/m³ increase in NO3 per 1,000,000 pregnancies
Week from birth in which exposure occurred

Figure 5.3: Results for NO_3, exposures anchored at conception (top) and lagged from birth (bottom). Risk differences for 1 µg/m3 increases in NO_3 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. "Single-pollutant" models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. "Multi-pollutant" models adjusted for previous factors and co-occurring elemental carbon, organic carbons, and sulfates. Exposures are anchored at time of conception (left panel) or time of birth and lagged (right panel). Outcomes are as follows: (a & e) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b & f) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c & g) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d & h) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

Preterm birth risk differences for a $1\mu g/m^3$ increase in SO_4 with exposures anchored at conception are shown in Figure 5.4. For SO_4 exposure in single pollutant models, ExPTB risks were generally null through week 10 of gestation, then increasing through week 20 (Figure 4a). Risks for VPTB, MPTB, and LPTB were generally elevated across all weeks of gestation, except for weeks very early in gestation for MPTB and LPTB outcomes (Figure 5.4b-d). Risks were similar between single- and multi-pollutant models.

With lagged exposures of SO_4 anchored at birth, preterm risk differences were generally similar between single- and multi-pollutant models. For ExPTB and VPTB, all risks were inverse to null (Figure 4e and 4f). For MPTB and LPTB, elevated risks were observed with lags 0-2, followed by null risks (Figure 4g and 4h).


a
ExPTB
100
80
60
40
20
0
-20
-40
1 3 5 7 9 11 13 15 17 19
Single-pollutant
Multi-pollutant
b
VPTB
150
100
50
0
-50
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
300
250
200
150
100
50
0
-50
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
600
400
200
0
-200
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred
Risk differences for 1μg/m3 increase in SO4 per 1,000,000 pregnancies

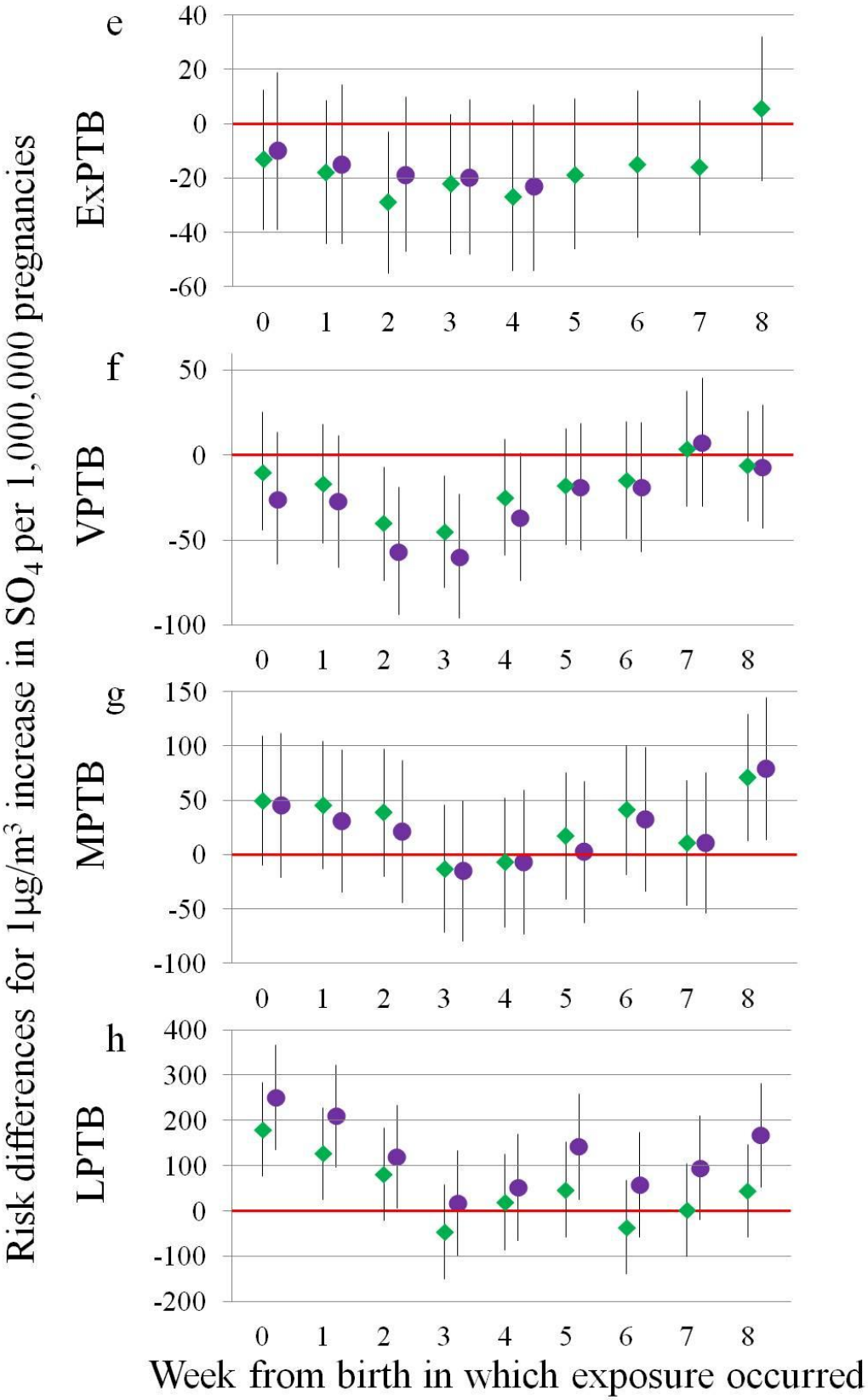
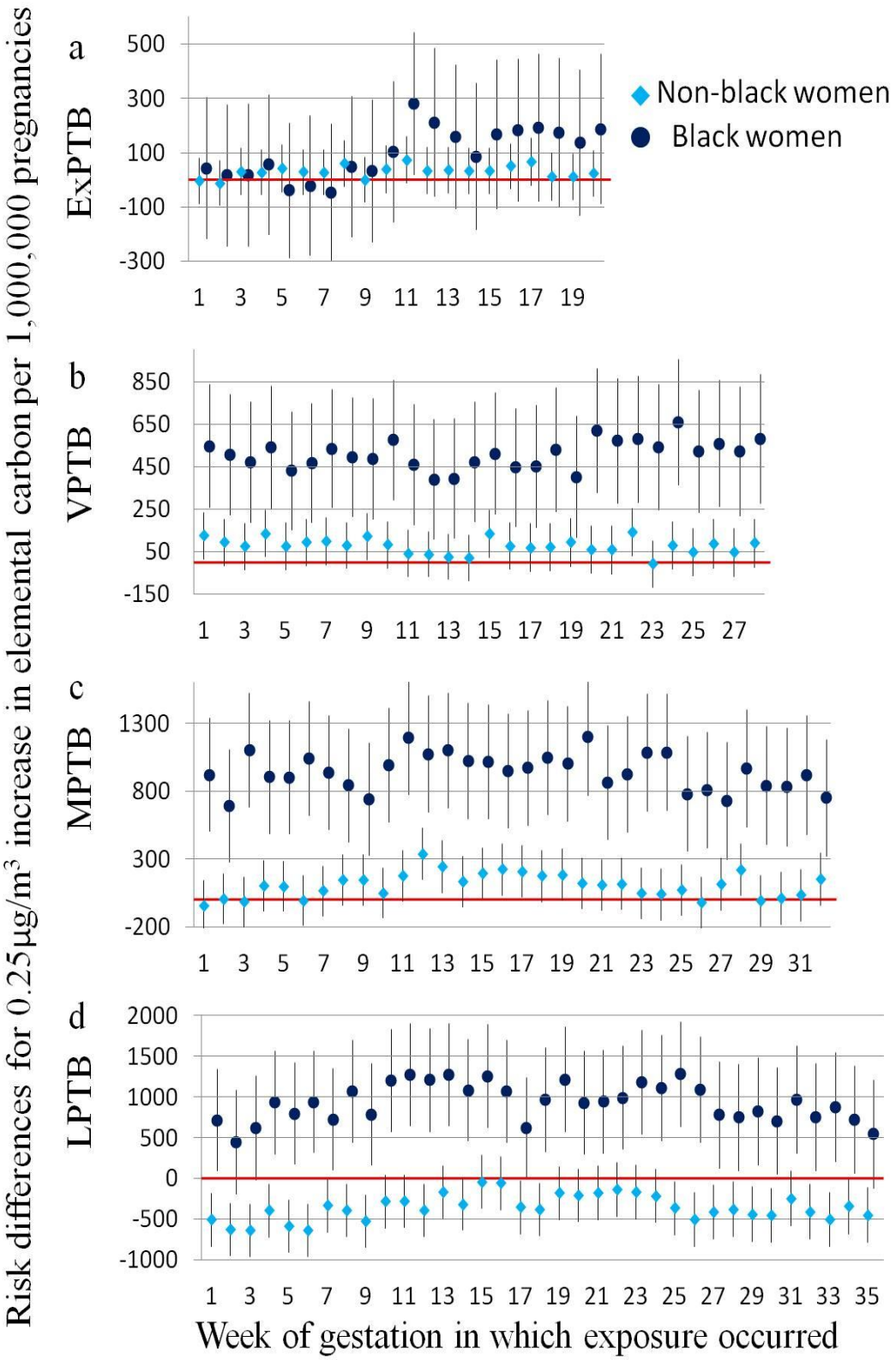

e
ExPTB
40
20
0
-20
-40
-60
0 1 2 3 4 5 6 7 8
f
VPTB
50
0
-50
-100
0 1 2 3 4 5 6 7 8
g
MPTB
150
100
50
0
-50
-100
0 1 2 3 4 5 6 7 8
h
LPTB
400
300
200
100
0
-100
-200
0 1 2 3 4 5 6 7 8
Risk differences for 1μg/m3 increase in SO4 per 1,000,000 pregnancies
Week from birth in which exposure occurred

Figure 5.4: Results for SO_4, exposures anchored at conception (top) and lagged from birth (bottom). Risk differences for 1 µg/m3 increases in SO_4 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. "Single-pollutant" models (green diamond) adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. "Multi-pollutant" models (purple circle) adjusted for previous factors and co-occurring elemental carbon, organic carbons, and nitrates. Exposures are anchored at time of conception (left panel) or time of birth and lagged (right panel). Outcomes are as follows: a & e) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b & f) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c & g) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d & h) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

Effect Measure Modification

No modification of risk estimates was observed for any species by infant sex or maternal parity. Risk differences for elemental carbon exposure and VPTB, MPTB, and LPTB were higher than would be expected on an additive scale for women of black race and women who smoked during pregnancy (Figure 5). Some modification of effects with race and smoking status were observed with OC exposures, though these were less consistent across outcome categories (supplemental figure). No effect measure modification by race or smoking was observed for NO_3 or SO_4.


Risk differences for 0.25µg/m³ increase in elemental carbon per 1,000,000 pregnancies
a
ExPTB
500
300
100
-100
-300
1 3 5 7 9 11 13 15 17 19
Non-black women
Black women
b
VPTB
850
650
450
250
50
-150
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
1300
800
300
-200
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
2000
1500
1000
500
0
-500
-1000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred

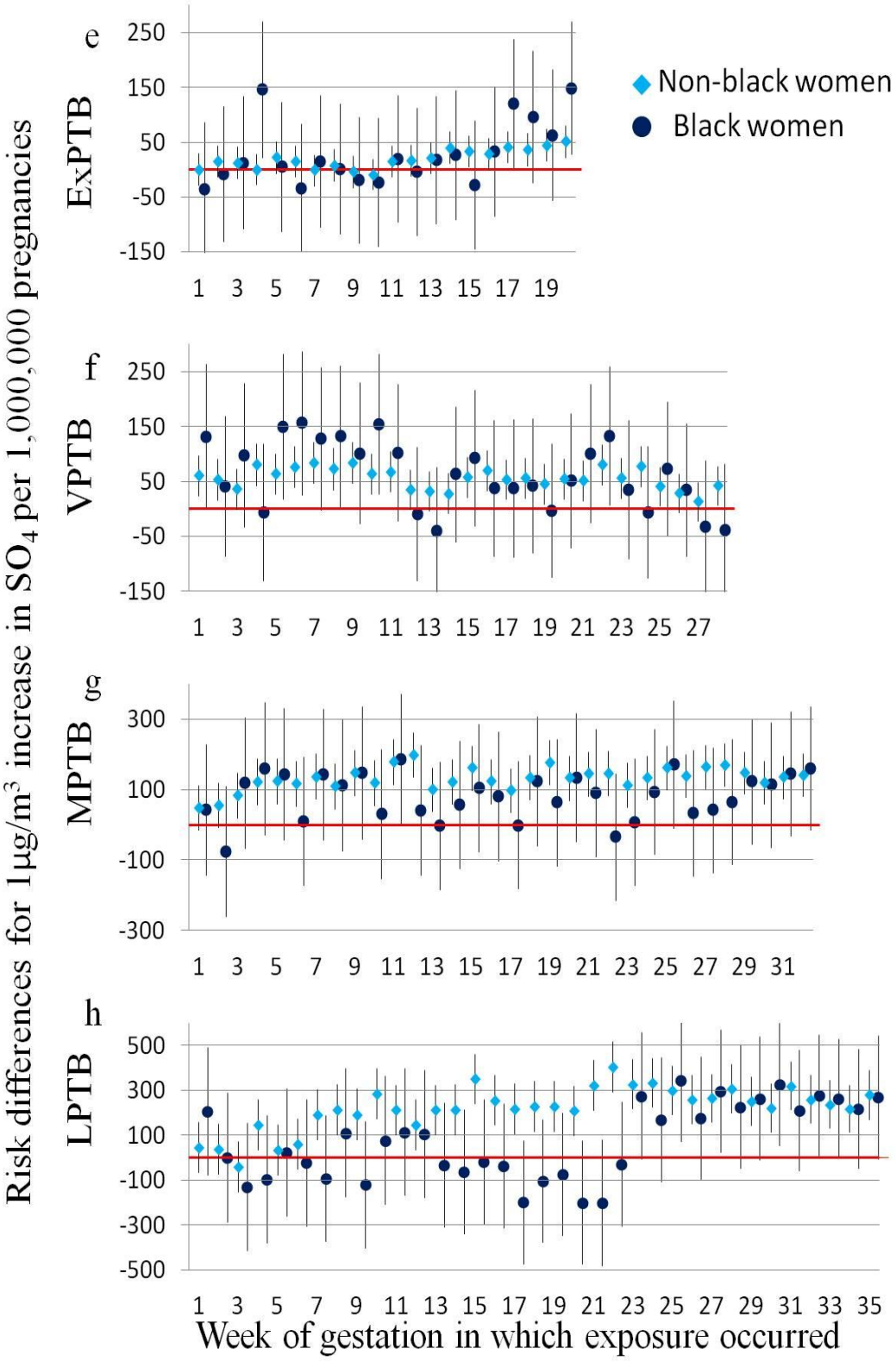

e
ExPTB
250
150
50
-50
-150
1 3 5 7 9 11 13 15 17 19
Non-black women
Black women
f
VPTB
250
150
50
-50
-150
1 3 5 7 9 11 13 15 17 19 21 23 25 27
g
MPTB
300
100
-100
-300
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
h
LPTB
500
300
100
-100
-300
-500
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred
Risk differences for 1μg/m³ increase in SO4 per 1,000,000 pregnancies

Figure 5.5: Effect measure modification by black race for elemental carbon (top, present) and SO_4 (bottom, no modification). Risk differences for 0.25μg/m^3 increases in EC and 1μg/m^3 increases in SO_4 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for maternal education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at time of conception. Outcomes are as follows: (a & e) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b & f) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c & g) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d & h) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

5.5 Discussion

Our findings support a role for $PM_{2.5}$ species in risk of PTB, with the potential for different effects at various gestational ages and during diverse windows of exposure. We found risk differences varied by exposure window and outcome period. EC appeared most influential in VPTB and MPTB, particularly with exposure windows before the 23rd week of gestation and with lags of up to 4 weeks. EC also demonstrated EMM with race (black v. non-black) and smoking status wherein RDs among black women were much higher than among non-black women, with smoking status following a similar pattern. We observed negative risk differences with OC for exposure windows anchored at conception, but only in LPTB outcomes or multi-pollutant models. As it is unlikely OCs have a protective health effect, this may be due to model error/inefficiency (e.g., in multi-pollutant models where EC has a higher effect, OC has a lower effect, possibly an artifact of high correlation between the two). It is also possible that due to correlation, when both EC and OC are present in models a sparse data problem arises. If so, we would expect to see risks moving away from the null, perhaps extensively, leading to biased risks and interpretations. Other potential explanations for the negative risk differences observed

include the possibility of interactions between EC and OC and non-linear effects. NO_3 was associated with increased risk of PTB with lagged exposures and exposures in weeks of the 1st trimester with multi-pollutant models. SO_4 shows increased risks for PTB across categories of gestation and with most exposure windows. SO_4 appears to have a role in risk of PTB, though no particular windows of vulnerability emerged from our analysis.

Differences between single- and multi-pollutant models indicate that there is some confounding between species, though not for every pollutant. Risk differences for SO_4 exposure do not change between single- and multi-pollutant models. This could mean that effects of SO_4 are unconfounded by the effects of the other species. Or it may be that SO_4, which makes up most of the $PM_{2.5}$ mass in the study area (northeast US) is serving as a proxy for $PM_{2.5}$ mass effects. Single pollutant models are not invalid due to confounding but should be interpreted as reflecting effects beyond the one pollutant in the model. For example, a single-pollutant model of EC will also carry with it some of the effects of OCs. This is due to the high correlation between the two species as they are produced by a number of the same processes and sources. As a corollary, single-pollutant models may still show some regional differences in effect as they are likely to carry some of that variation with them.

Though mechanisms of action for $PM_{2.5}$ species on preterm birth are poorly understood at present, likely contenders are inflammatory or oxidative stress processes. $PM_{2.5}$ exposure has been linked to increased markers of systemic inflammation in humans and changes in placental morphology in mice, which may be a consequence of inflammation.(Backes et al. 2013; Lee et al. 2013; Veras et al. 2008) Changes in the placenta may lead to inadequate placental perfusion or impaired nutrient

exchange.(Kannan et al. 2006) Inflammation may also lead to the creation of reactive oxygen species, which can cause cell damage, DNA damage, disruption of cellular processes, irreversible protein modifications, or alternations in cellular signaling.(U.S.EPA. 2009) It is not known if these specific processes would lead to PTB, however they are all alterations of normal function and may disrupt the normal processes of gestation.

Each species has properties that make it potentially harmful, though again these pathways are poorly understood for pregnancy outcomes. Elemental carbon may directly induce a health response or may bear other toxic chemicals that induce inflammation.(Ritz and Wilhelm 2008) Effect measure modification effects observed with race and smoking status may indicate priming effects by exposure to the pollutants in cigarette smoke and the social stressors we believe race represents.

Effects observed with OC exposures should be interpreted with caution, as the modeling of OCs is somewhat restricted by lack of inclusion of secondary formation of OCs. This gives the OC concentrations an unexpectedly high correlation with EC (which is formed only through primary processes (i.e., emissions)), and effects may be unduly influenced by this correlation. The epidemiology and toxicological literature lacks discussion of the role of nitrates and sulfates on birth outcomes. However, some possibilities may be extrapolated from other air pollution literature indicating that they mediate inflammatory processes.(Bind et al. 2012) The area of $PM_{2.5}$ species and preterm birth has received limited attention, though it is likely that toxicity of $PM_{2.5}$ species influence $PM_{2.5}$'s effects on preterm birth.

No other studies of $PM_{2.5}$ species have examined effect measure modification. Our finding of excessively high risk differences for women of black race compared to non-black women is not likely to be a biological effect of race, but rather a priming effect of those factors that race represents (e.g., stress due to institutionalized racism). In this situation such negative factors would deplete a woman's resources for dealing with the insults offered by EC, and so EC would have a much worse effect on health. In other words social stressors related to race in the United States may create an "allostatic load" in which a woman has long term biological dysregulation due to the continuous or frequently occur presence of stressors.(McEwen and Seeman 1999) This allostatic load then prevents women from responding appropriately (in a biologic sense) to further stressors such as air pollutants. Smoking likely works in a similar, though more direct and biological, manner. Particulates in cigarette smoke offer an initial insult, which may overwhelm a woman's protective/coping processes, and EC exposure adds an additional insult that then has no barrier to adverse effects. These pathways are plausible, but there has been little research on this topic.

Currently, only four studies are published on the influence of $PM_{2.5}$ species on preterm birth, with a variety of study designs, exposures, and exposure assessments between them.(Brauer et al. 2008; Darrow et al. 2009; Gehring et al. 2011; Wilhelm et al. 2011) Two studies used land use regression (LUR) methods to examine the effects of soot or black carbon (a close but not complete corollary to elemental carbon). Brauer et al.(2008) found no effect of black carbon with entire pregnancy exposures, while Gehring et al.(2011) found positive odds ratios with entire pregnancy and last month exposures. Brauer et al.'s(2008) LUR model performed poorly in evaluation tests and used $PM_{2.5}$

data for temporal adjustment, as only annual black carbon data was available. Gehring et al.(2011) did not account for spatial variation of soot/$PM_{2.5}$ between 1999/2000, years when the environmental data were available, and 1996/97, years when the pregnancies were studied. Our study shares a cohort study design with these studies but uses different exposure assessment methods. While the LUR models offered advantages in detection of spatial heterogeneity of air pollutants, our use of the bias-corrected CMAQ model offered other benefits. First, our study area was not limited to a monitor rich area, and thus our study population is much larger and less selective. Our CMAQ model was also constructed using validated methods and data current to the timing of pregnancies in our study population. The possibility also exists that these LUR studies may retain some regional variation in pollutant mixtures, as they examined only single pollutants and co-pollutants were highly correlated.

Two further studies each examined a variety of $PM_{2.5}$ species. In a time-series study of the Atlanta area, Darrow et al.(2009) observed positive risk ratios for nitrates and sulfates with exposure in the 1st month of pregnancy and for sulfates and EC with a 1 week lag from birth. OCs had null effects for all exposure windows examined. Given the differences in study design and exposure assessment (use of a single monitor for $PM_{2.5}$ species ascertainment), our results are fairly congruent with the results from Darrow et al.(2009). Differences between our results do occur; for example, with EC exposures in early pregnancy we found elevated risks, though not for all PTB categories. Wilhelm et al.(2011) used a case-control design with entire pregnancy exposures and found elevated odds ratios with exposure to EC, OC, and ammonium nitrate in single pollutant models and ammonium nitrate in multi-pollutant models. Odds were null for ammonium sulfate

in single-pollutant models and inverse in multi-pollutant models. With the dense monitoring network used for species analyses, it is likely that Wilhelm et al.(2011) better characterized spatial heterogeneity in $PM_{2.5}$ species than the CMAQ model. However, Wilhelm et al.(2011) only reported on whole pregnancy exposure, whereas we were able to examine weekly exposure windows throughout pregnancy.

In addition to examining weekly exposure windows and the use of monitor-corrected CMAQ models, our study diverges from previous literature with examination of effect measure modification, risk difference as the measures of effect, and use of refined categories of preterm birth. Preterm birth captures a 4 month period across pregnancy in which development occurs rapidly. Those births ending in the earliest weeks of this period are also those with the most severe health outcomes and lifetime costs. By examining categories of preterm birth, rather than as a single outcome, we can highlight the associations specific to each gestational age. It is plausible that there are different underlying etiologies of birth across the 4 month period of gestation, and these potential differences should be considered when examining preterm birth as an outcome of interest.

Preterm birth may have disparate etiology based on gestational week, as fetal development and vulnerabilities shift rapidly. This is supported in our analysis, as we observed different effects based on category of preterm birth, and which may have been masked by collapsing PTB categories may. The two types of exposure windows examined (anchored at conception or lagged from birth), also offer insight into the potential for differing mechanisms. Exposures anchored at conception investigate the possibility of developmental insult caused by exposure to $PM_{2.5}$ species and the potential

for mechanisms that act across the length of gestation. Exposures lagged from birth instead investigate the possibility of a more acute effect of $PM_{2.5}$ species, wherein the pollutants act as triggers for the cascade of events leading to labor and birth. Both mechanisms are plausible and have found support in the body of research examining broader PM and PTB associations. However, exposure windows anchored at conception have the advantage of comparing pregnancies at identical gestational ages, rather than having gestational ages be outcome-dependant. Our large population allowed us to examine potential effect measure modifiers, providing insight into possible vulnerable populations. We chose risk differences as our effect measure because they represent absolute change in risk from which a number need to harm (NNH = 1/RD) may be calculated. These measures better depict public health impact than relative measures of risk.

As with many studies of air pollution, classification of exposure is imperfect. Even with bias correction, the models used to estimate pollutant concentrations are limited. This is particularly true with the $PM_{2.5}$ species, for which monitoring networks remain sparse, and the monitoring of a particular species may be inconsistent across monitoring sites. For example, CMAQ models (uncorrected) are known to underperform for prediction of OC concentrations; bias correction can improve OC estimates, but high uncertainty for predictions remains as the distance between monitors is large and the same measurement methods are not used at all sites.(Hogrefe et al. 2009) While all models have performance issues to some degree, the concentration estimates produced by CMAQ models allow for the estimation of health effects across large areas/populations, whereas health effect estimation with only monitoring networks is much more

constrained, particularly for $PM_{2.5}$ species. Beyond limitations specific to the use of models, potential exposure classification issues include: the use of ambient rather than personal measures of $PM_{2.5}$ species and using a single residential point for exposure assignment rather than a profile of where a woman's time is spent – including indoor versus outdoor exposure and the assumption that women had a single residence throughout pregnancy. Though these factors are likely non-differential by outcome, their consequences may be complicated, leading to responses that may be biased toward or away from the null depending on if observed exposures were lower (i.e., she works in a highly polluted area) or higher (i.e., she spends more time indoors) than true exposures. While having individual level exposures would be beneficial, we can interpret the observed results as effects of ambient exposures, which are most likely to be affected by changes to air pollution regulations.

This study identified associations between average weekly exposure to EC, OC, NO_3, and SO_4 during gestation and risk of four categories of preterm birth for women residing in OH, PA, or NJ from 2000 to 2005. EC and SO_4, among the best characterized of the $PM_{2.5}$ species, had the most consistent associations with risk of preterm birth in both single- and multi-pollutant models. Differences existed not only between $PM_{2.5}$ species, but also with different windows of exposure and preterm birth at specific gestational ages. These results indicate diverse periods of action for the species of PM, along with differing windows of vulnerability for the risk of various degrees of PTB. Future studies of particulate matter and its components should carefully assess timing of exposure and extent of preterm gestational age under investigation.

This work does not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Chapter 6: Discussion

This study examined the associations between $PM_{2.5}$ mass and $PM_{2.5}$ species for weekly windows of exposure during pregnancy and the risk of preterm birth at four categories of gestational age using an exposure assessment method that offers complete spatial and temporal coverage for our study area and period. We estimated risk differences for increases in $PM_{2.5}$ mass, elemental carbon, organic carbons, nitrate, and sulfate for exposure windows throughout gestation and lagged from birth. Observed effects varied by exposure window, outcome period, and pollutant.

6.1 Summary of effects

To accomplish the first aim, we examined exposure to $PM_{2.5}$ mass during pregnancy and estimated risk differences for a 1$\mu g/m^3$ increase in average weekly windows of exposure across pregnancy. We observed positive risk differences for $PM_{2.5}$ mass exposure, particularly in early gestational weeks and lagged exposures near time of birth. Our results were consistent with previous studies of $PM_{2.5}$ mass and preterm birth, despite a number of differences between our study and those previous. In particular, seven studies across different geographic areas have reported positive effect estimates with exposure to $PM_{2.5}$ mass in early pregnancy.(Chang et al. 2012; Hansen et al. 2006; Huynh et al. 2006; Jalaludin et al. 2007; Lee et al. 2013; Ritz et al. 2007; Warren et al. 2012) Several studies have reported positive odds ratios for exposures late in pregnancy

or near birth.(Chang et al. 2012; Gehring et al. 2011; Hansen et al. 2006; Wilhelm and Ritz 2005) However, three studies have found null or inverse effects for these periods as well.(Darrow et al. 2009; Gehring et al. 2011; Wilhelm and Ritz 2005) Studies of whole pregnancy exposure report generally positive effects.(Brauer et al. 2008; Gehring et al. 2011; Huynh et al. 2006; Kloog et al. 2012; Wilhelm et al. 2011; Wu et al. 2009; Wu et al. 2011) Comparing studies of $PM_{2.5}$ mass and preterm birth is somewhat difficult due to the myriad differences existing between studies. One of the potentially major issues is that composition of $PM_{2.5}$ is likely to vary across geography and time such that exposures to $PM_{2.5}$ mass may not mean the same thing in different studies. While it should be noted that there may be health effects due to the properties of $PM_{2.5}$ mass outside of species toxicity, variation in magnitude of effects observed across space and time may be explained in part by $PM_{2.5}$ composition.

To accomplish the second aim of this study, we examined exposure to elemental carbon, organic carbons, nitrate, and sulfate during pregnancy and estimated risk differences for either 0.25μg/m^3 (EC) or 1μg/m^3 increases in average weekly windows of exposure across pregnancy.

EC appears most influential in VPTB and MPTB, particularly with exposure windows before the 23rd week of gestation and with lags of up to 4 weeks. EC also demonstrated EMM with race (black v. non-black) and smoking status, wherein RDs among black women were much higher than among non-black women with smoking status following a similar pattern. Of the four previous studies that examined EC exposure, the two that used monitor-based exposure assessment found increased risk of preterm birth for all pregnancy windows (Wilhelm et al. 2011) and with a 1-week lag

from birth (Darrow et al. 2009). A study that used modeled black carbon (a close corollary of EC) exposures had similar findings, with increased odds for entire pregnancy and month before birth exposures.(Gehring et al. 2011) We have similar findings, particularly for VPTB and MPTB outcomes and with models adjusting for other $PM_{2.5}$ species. Another study that used modeled black carbon found no changes in odds for entire pregnancy exposures, which may be in part due to the quality of their black carbon models, which were unable to be successfully validated.(Brauer et al. 2008) No other studies of $PM_{2.5}$ species have examined effect measure modification. Our finding of excessively high risk differences for women of black race compared to non-black women is not likely to be a biological effect of race, but rather a priming effect of those factors that race represents (e.g., stress due to institutionalized racism). In this situation, such negative factors would result in biological dysregulation and increased allostatic load(McEwen and Seeman 1999), depleting a woman's ability to respond appropriately to the insults offered by EC. Consequently, EC would have a much worse effect on health. Smoking likely works in a similar, though more direct and biological, manner. In that particulates in cigarette smoke offer an initial insult, which may overwhelm a woman's biological protective processes (such as detoxification), and EC exposure adds an additional insult with no barrier to adverse effects. These pathways are plausible, but there has been little research on this topic.

For OC exposure windows anchored at conception, we observed null and negative risk differences. The negative risk differences were only in LPTB outcomes or multi-pollutant models. Darrow et al.(2009) found similar null results for all exposure windows in their time-series study using a single monitor. However, in a study that employed a

dense monitoring network, Wilhelm et al.(2011) found increased odds with entire pregnancy exposure to OCs. As it is unlikely OCs have a protective health effect, results in our study may be due to modeling error or inefficiency and should be interpreted cautiously. The CMAQ models we use are known to under-perform in certain aspects; one of those is the modeling of secondary formation of OCs, a substantial contributor to OC concentration. Therefore the concentrations used in our models are from only primary sources (i.e., emissions). This also leads to the high correlation with EC, whereas a lower correlation would be expected. Changes observed between single- and multi-pollutant models may be due to this high correlation (i.e., as the effect of EC goes up, the effect of OC goes down to compensate). It is also possible that when both EC and OC are present in models a sparse data problem arises due to correlation. If so, we would expect to see risks moving away from the null, perhaps extensively, leading to biased risks and interpretations. OCs are also a mixture of many compounds rather than a single substance. Thus effects observed are those for a particular mixture of compounds and may share some of the same problems as studying $PM_{2.5}$ mass. Other potential explanations for the negative risk differences observed include the possibility of interactions between EC and OC and non-linear effects. While these explanations are all possible and may be acting concurrently, the most likely explanation remains that OCs are poorly estimated by the CMAQ model employed here. Given this, the observed risks for OCs should be interpreted with extreme caution, if at all. While null and negative risks were observed here between OCs and PTB, this association is still worthy of study, particularly given the relatively poorer characterization of OC concentrations with this

CMAQ model compared to the measured concentrations for Wilhelm et al.(2011) where positive associations were observed with exposure to OCs and PTB.

The epidemiology and toxicology literature lacks discussion of the role of nitrates and sulfates on birth outcomes. However, some possibilities may be extrapolated from other air pollution literature indicating they mediate inflammatory processes.(Bind et al. 2012) In our study, NO_3 was associated with increased risk of PTB with all lagged exposures and exposures in the 1st trimester with multi-pollutant models. In two previous studies, Darrow et al. observed positive risk ratios for nitrate with exposure in the 1st month of pregnancy, and Wilhelm et al. observed elevated odds ratios with entire pregnancy nitrate exposures in both single- and multi-pollutant models.(Darrow et al. 2009; Wilhelm et al. 2011) Our analyses of SO_4 exposure show increased risks for PTB across categories of gestational age and with most exposure windows. SO_4 appears to have a solid role in risk of PTB, though no particular windows of vulnerability emerged from our analysis. Our findings for sulfate exposures are inconsistent with those from the two other studies; Darrow et al.(2009) observed positive risk ratios with exposure in the 1st month of pregnancy and with a 1 week lag from birth (i.e., specific windows emerged), and Wilhelm et al.(2011) found null effects in single pollutant models and negative effects in multi-pollutant models.

In examination of risk differences with both single-and multi-pollutant models, in which species were entered into the model as the sole exposure or all entered simultaneously, there does appear to be some indication of confounding by other species. Though effects were not shifted at all exposure windows, there were instances in which controlling for exposure to co-species led to dramatic changes in risk differences,

offering insight into the specific toxicity of a particular species. Risk differences for SO_4 exposure do not change between single- and multi-pollutant models. This could mean that effects of SO_4 are unconfounded by the effects of the other species, or it may be that SO_4, which makes up most of the $PM_{2.5}$ mass in the study area (northeast US) is serving as a proxy for $PM_{2.5}$ mass effects. Single pollutant models are not invalid due to confounding but should be interpreted as reflecting effects beyond the one pollutant in the model. For example, a single-pollutant model of EC will also carry with it some of the effects of OCs due to the high correlation between the two species, which are produced by many of the same primary sources. As a corollary, single-pollutant models may still show some regional differences in effect, as they are likely to carry some of that variation with them.

Most negative risks observed occurred in later categories of PTB. This may indicate a sort of "healthy worker" or harvesting effect, wherein those pregnancies that were most vulnerable to the effects of $PM_{2.5}$ exposure remove themselves (through preterm labor) at earlier gestational ages. Therefore, in the later gestational ages there is the effect of examining a population that is "healthier" than had all pregnancies continued through this time period. This potential explanation for observed risks may be explored by looking at effects of smoking in older cohorts, where we might expect "less healthy" pregnancies to be more susceptible to the health effects of smoking, and seeing if a similar pattern emerges.

6.2 Potential mechanisms

The observed effects for exposures anchored at conception and those lagged from birth support the potential for multiple mechanisms of action. Effects observed at specific gestational periods may indicate that $PM_{2.5}$ (mass or species) is causing a developmental insult that increases risk of preterm birth during certain periods of heightened vulnerability. Whereas, effects observed in lagged windows of exposure may be the result of the fetus producing pro-inflammatory cytokines, which can trigger the cascade of events leading to labor and birth. There may also be mechanisms that bridge windows of exposure. For example, nutritional deprivation of the fetus may occur across gestation through disruption of placental implantation at the beginning of pregnancy or placental function/nutrient transport throughout pregnancy. These mechanisms are all plausible and have found support in the body of research examining PM and PTB. However, mechanisms associated with exposure windows anchored at conception have the advantage of comparing pregnancies at identical gestational ages rather than having gestational ages be outcome-dependant.

Though mechanisms of action for $PM_{2.5}$ mass and species on preterm birth are poorly understood at present, likely contenders are inflammatory or oxidative stress processes. $PM_{2.5}$ exposure has been linked to increased markers of systemic inflammation in humans and changes in placental morphology in mice which may be a consequence of inflammation.(Backes et al. 2013; Lee et al. 2013; Veras et al. 2008) Changes in the placenta may lead to inadequate placental perfusion or impaired nutrient exchange.(Kannan et al. 2006) Impaired nutrition may in turn result in fetal distress leading to initiation of labor as a defense mechanism. Inflammation may also lead to the

creation of reactive oxygen species, which can cause cell damage, DNA damage, disruption of cellular processes, irreversible protein modifications, or alternations in cellular signaling.(U.S.EPA. 2009) Further research into the toxicologic effects of $PM_{2.5}$ mass and species on preterm birth would be beneficial to understanding of the observed epidemiologic associations, in particular, improved understanding of placental implantation and development and how $PM_{2.5}$ might act on or interact with the many pathways leading to preterm birth.

6.3 Strengths

Utilizing bias-corrected CMAQ model predictions to estimate $PM_{2.5}$ concentrations eliminated temporal and spatial gaps in exposure data, a common issue with monitors that are not always active and sparse outside of densely populated areas. Accordingly, all pregnancies in the three state study area over the 6 year study period had the potential for inclusion, an improvement over studies that must rely upon mothers residing in close proximity to air monitors. The more complete study population improves generalizability of our study results, as women who live in suburban and rural areas are included. Our considerable study population included nearly 2 million pregnancies in the analytic population. The size of our analytic population allowed for examination of effect measure modification by several factors, and detection of very small effects.

We also had the ability to examine four $PM_{2.5}$ species. The number of monitors for $PM_{2.5}$ species is limited; therefore, the ability to examine them over a large spatial area is unusual. The large study area insured both spatial and temporal variability in

species concentrations. Examining $PM_{2.5}$ species gives insight into the potential drivers of health effects of $PM_{2.5}$, and with our large study population, we were able to examine not only main effects but also effect measure modification.

Our use of small windows of exposure and categorization of preterm birth by specific gestational ages was another positive aspect of our study. The weeklong windows of exposure let us identify specific vulnerable periods in development, aiding in the elucidation of potential mechanisms of action. Only one other study(Warren et al. 2012) has examined such small windows of exposure. Smaller windows of exposure are likely to be less stable than larger windows, such as months or trimesters. However, they give more insight into etiologic processes occurring. For example, an effect observed with 1st trimester exposure might lead one to explain that PM early in pregnancy increases risks of PTB. Whereas, with an effect observed at week 4-5, one might offer the explanation that increases in exposure to PM around the time of expected implantation increase risk of PTB, suggestion than placental development is affected by PM. This gives richer and more detailed evidence, allowing for better consideration of $PM_{2.5}$'s potential mechanisms leading to preterm birth.

Development occurs rapidly during pregnancy, and births that occur at earlier weeks of gestation may be fundamentally different from those at later weeks. Although they are both preterm, there may be alternate etiologic pathways operating for pregnancies that end at different ages. For example, infection and susceptibility to infection may be more important for births at the earliest gestational ages, while placental development may be important for the middle categories of preterm birth and triggering

mechanisms or sustained nutritional deprivation may be more relevant to those pregnancies that continue through the later preterm gestational ages.

Finally, the use of risk differences as the effect measure of interest is a strength, as these absolute measures of risk are more easily interpretable and can be simply transformed into a number need to harm (NNH = 1/RD) which provides information about how changes to the exposure would be expected to affect public health.

6.4 Limitations

Like most studies of air pollution and preterm birth, we have relied on imperfect exposure classification, and the results may reflect residual or unmeasured confounding. Exposure misclassification may be due to the use of a model for exposure assessment (even with bias correction, a model is only as good as its input), the use of ambient rather than personal data, the use of a single residential point rather than a profile of where a woman's time is spent, and the assumption that women do not change residence throughout pregnancy. These factors would likely be nondifferential by outcome, though not necessarily by confounding factors (e.g., race). Assessing the effect of these potential errors on observed effects is somewhat complicated. Up to 33% of women move during pregnancy.(Canfield et al. 2006; Chen et al. 2010) Though many women move to areas with similar pollution and socio-demographic characteristics, it is likely that women of lower socioeconomic class move more often and may gravitate towards areas of poorer environmental quality and higher air pollution than women of other classes.(Chen et al. 2010; Lupo et al. 2010; Madsen et al. 2010; Miller et al. 2010) Should this scenario occur, $PM_{2.5}$ at the birth residence would be higher than during earlier pregnancy and

may shift effects toward the null. In a separate scenario, if a woman works in an area with higher pollution or spends a large amount of time commuting, her observed exposure may be lower than her true exposure, thus potentially biasing her observed response toward the null. Or a woman might spend most of her time indoors, information not captured by our data, and her true exposure may be lower than her observed exposure, thus potentially biasing her observed response away from the null.(Allen et al. 2012; Hodas et al. 2012) Unfortunately it is impossible to know what the true exposure conditions are for every woman. Interpretatively, we focus on the effect of ambient exposures, which are also those most likely to be affected by changes in policy regarding air pollution.

Bias due to residual or unmeasured confounding may arise from the use of proxy variables for socio-economic status or the lack of an important contributing variable. Socio-economic status is not well defined. While the variables we use to approximate SES factors are commonly used in this manner, they may not fully capture the influence of socioeconomic status on the $PM_{2.5}$/PTB association. Again, it is difficult to say exactly how these factors might affect our estimates. If confounder measurement is poor it may be moving estimates towards the null, so better measurement might increase real risks. If confounders are unmeasured and they should be included, estimates may be higher than they should be.

The study population is, at best, an approximation of all pregnancies at risk of preterm birth, as fetal deaths are excluded due to differential reporting of maternal addresses by state. Given the relatively small number of fetal deaths (10,413 fitting the most basic criteria of having a gestational age between 20-44 weeks, singleton, no

congenital anomalies), it is unlikely that fetal deaths would have a strong impact on the analyses performed. However, these pregnancies do constitute a part of the cohort of pregnancies at risk of preterm birth. Therefore it is useful to consider their potential impact should they have been included in the analyses. Fetal deaths are likely to have myriad causes, even more so than preterm birth. It may be that adding fetal deaths to the study population would merely have the effect of a slight improvement to precision. However, if the causes of fetal death are not shared with preterm birth (a scenario which is likely to be at least partially true, with some causes shared and others separate), then the addition of fetal deaths might lower precision. If, as some researchers have suggested, fetal deaths are the results of the highest exposures to $PM_{2.5}$, then adding fetal deaths to the study population would increase observed risks. However, given fetal death distribution across gestational ages and the small risks observed for preterm birth, this scenario seems unlikely.

Measurement of gestational age is also likely to include misclassification. In this analysis clinical estimates of gestational age were used, but these measures are not without issue. Clinical estimates are most accurate if done by ultrasound before 20 weeks of gestation. However not all women get an ultrasound before the 20^{th} week of pregnancy, and this is likely to be differential by socio-economic status. In addition, while pre-20 week ultrasound is the best method, other methods including clinician estimate at time of birth and ultrasounds occurring after 20 weeks are used, and the method used to determine gestational age is not recorded on the birth certificate. In using clinical estimate of gestation for both outcome determination and exposure assignment, the potential for misclassification indicates the need for some flexibility in interpretation

of results, as these measures are not of pinpoint accuracy. Classification of births at the earliest weeks as preterm is likely appropriate. However births at near-term and late preterm weeks may be inappropriately classified. Therefore, some caution should be taken when interpreting the observed effects for the LPTB category, as there may be conflation between these births and near term births.

6.5 Public health impact

Detecting the exposures that contribute to preterm birth offers the opportunity to address those causes and reduce preterm birth and other adverse outcomes. Everyone must breathe the air and so everyone is in some measure exposed to air pollution. The ubiquitous nature of particulate matter means exposure increases the potential for harm, even when effect magnitudes are small. It is not possible to remove people from the need to breathe or even to remove them from the most polluted locales (e.g., urban areas). Therefore, interventions must be targeted at removing (or at least lowering) the concentrations of pollutants in the air. This is done primarily through regulatory actions, which require substantial evidence to enact. Our study offers further evidence of the adverse health effects of $PM_{2.5}$ mass and species. Increasing the base of knowledge on the adverse health effects associated with exposure to $PM_{2.5}$ mass and species allows for more informed decision making when setting new regulatory standards, including information on pregnant women and infants as a potentially vulnerable subpopulation. Preterm birth captures a 4 month period across pregnancy in which development occurs rapidly. Examining categories of preterm birth let us observe the differing magnitudes and patterns of risks associated with $PM_{2.5}$ mass and species exposure at specific

gestational ages. The differing patterns of risk observed may affect how we consider the etiology and long term health effects of preterm birth, and in turn the formation of policies related to air pollution control. Even small increases in risk can have a large impact on some groups, such as the earliest preterm births. These births are more likely to result in infant mortality, developmental disorders, and have higher associated costs than even other preterm births. (Behrman and Butler 2007) The observed effects in the earliest preterm births, though small, may have a disproportionate effect on public health. Our study has assisted in marking the species of $PM_{2.5}$ that may be more responsible for adverse health effects, in improving knowledge about the effects of $PM_{2.5}$ at small windows of exposure over the entire course of pregnancy, and by examining potential differences in effect of $PM_{2.5}$ with preterm birth at varied gestational ages.

6.6 Future directions

There are several directions we might take to further our current work. One is to shift the question slightly. The questions asked in this work are about risk of birth at specific gestational ages. We might also ask whether $PM_{2.5}$ exposure shifts the time to birth, i.e., rather than moving a pregnancy to a different risk category, is a day or two shaved off of gestation. Another aspect that deserves further investigation is the use of models of $PM_{2.5}$ concentrations and how improvements and variations in these models affect health effect estimates. Further improvements in the models, such as better characterization of OCs and other species, smaller output grids, and addition of atmospheric processes generating pollutants, mean better exposure classification and may result in more accurate estimates of effect. In this work, we examined four species of

$PM_{2.5}$, but these are not the only components of $PM_{2.5}$ or properties of particulate matter that may be responsible for $PM_{2.5}$'s health effects. The nano fraction of particulate matter ($PM_{0.1}$) may be a large contributor, as these extremely small particles make up the greatest number of particles and can penetrate furthest into the body. There are also other components of $PM_{2.5}$, such as metals, that comprise a small percentage of $PM_{2.5}$ mass but may have large toxic effects.

In terms of research into the effects of $PM_{2.5}$ (and air pollution in general) on preterm birth, there are several areas where improvements could be made. Currently, potential mechanisms of action of $PM_{2.5}$ leading to preterm birth are mostly speculative, and many of the epidemiologic studies of $PM_{2.5}$ and preterm birth make no mention of mechanisms. There are few animal studies of $PM_{2.5}$ and preterm birth, and while there are clinical studies of the effects of $PM_{2.5}$ on specific immune responses, there are few specific links between those responses and the end result of preterm birth. Toxicologic or clinical studies that bridge the current gaps in knowledge for $PM_{2.5}$'s potential mechanisms of action would be highly beneficial, not only to our understanding of how $PM_{2.5}$ works, but also to our understanding of preterm birth. A major methodological concern in epidemiology studies of air pollution and preterm birth is the differences between actual personal exposure and the ambient exposures used to represent them. Ideally, researchers would have individual monitors for women for each day of pregnancy, and perhaps even before. Because measuring pollutant concentrations for a million or so women from conception until birth is vastly unfeasible, other solutions to personal exposure issues need to be considered. Modeling methods that use a small number of women to estimate patterns of behavior may be helpful. Similarly, if

measurements could be made of indoor air pollutants in different building types, correlations estimated between indoor and outdoor pollutant concentrations with various characteristics, and correlations between these factors and personal exposures estimated, then it is possible that women could be assigned propensities for concentrations given where they live and work.

6.7 Conclusion

$PM_{2.5}$ mass and species are associated with increased risk of birth at preterm gestational ages with exposure windows across pregnancy. There are differences in risk by pollutant studied, by gestational age of outcome, and by timing of exposure. This work contributes to the broader $PM_{2.5}$ and PTB literature by examining categories of preterm birth, weekly exposure windows across pregnancy, and $PM_{2.5}$ species: elemental carbon, organic carbons, particulate nitrate, and particulate sulfate. This study adds evidence for the adverse health effects of exposure to $PM_{2.5}$ in the subgroup of pregnant women.

Appendix A: Data acquisition and merging

Birth certificate data

Birth and fetal death records were requested through the internal review processes of PA, OH, and NJ. In PA, this process is handled by the Bureau of Health Statistics & Research of the PA Department of Health and involves an application form. Once access to data has been granted no further approvals are needed. In OH, the Ohio Department of Health Institutional Review Board reviews and approves the "Application for Protocol Review." The request is then sent to the Data Analysis manager of Vital Statistics data for processing. In NJ, approval of the data request must first be approved by the Data Steward of vital statistics data. Then an application including study protocol must be sent to the Department of Health Institutional Review Board for approval. After approval for the data requests was granted, each state sent data files to the Principle Investigator.

Fetal death records were acquired but not used in the reported analyses, due to the lack of maternal addresses for OH fetal death records. While this information is recorded and reported for NJ and PA, OH records are reported at no lower than municipal levels, meaning that exposure could not be assigned for these cases. Exposures were assigned to fetal deaths occurring in PA and NJ, and these records were retained for sensitivity analyses.

In PA, implementation of new birth certificates occurred during the requested time period. As such, 2 data files were obtained: one for years 2000-2002 with the older style of birth certificate data and one for years 2003-2005 with the newer style. Differences between styles were largely negligible for this study purpose. However, two variables (maternal educational attainment and maternal smoking during pregnancy) were

recorded in such a way as to require processing between the styles for accord in final datasets. For maternal education, the older style records years of education (1-17) while the newer style records highest level achieved (e.g., high school diploma, some college, bachelor's degree, etc.). To reconcile these variables categories of education matching the variable from the newer style of birth certificate were delimitated based on years of education. In the newer style of birth certificates women are asked to report average number of cigarettes smoked for each trimester and the 3 month period before pregnancy, whereas in the older style women are asked if they are smokers and if yes estimate number of cigarettes smoked per day. In this case, smoking status for women with the newer style of record was determined as having a reported average number of cigarettes during any period above 0. This left smoking as an ever-never variable for all women.

All observations were assigned a study ID and variables for each data file were constructed to be identical. This process was often simply to change a variable from character to numeric (e.g., for sex M=0 and F=1) and ensuring that all variable names were identical. The four data sets (two from PA due to change in birth certificate) were subset to create a single birth certificate dataset.

CMAQ data

Bias-corrected CMAQ output data was provided by Valerie Garcia and EPA's Atmospheric Modeling and Analysis Division. Datasets contained daily estimates for $PM_{2.5}$ mass and species, ozone, and temperature at each grid center point for 2000-2005.

Appendix B: $PM_{2.5}$ supplemental analyses, figures and tables

This index contains tables associated with figures shown in Chapter 4 and figures for supplemental analyses involving $PM_{2.5}$.

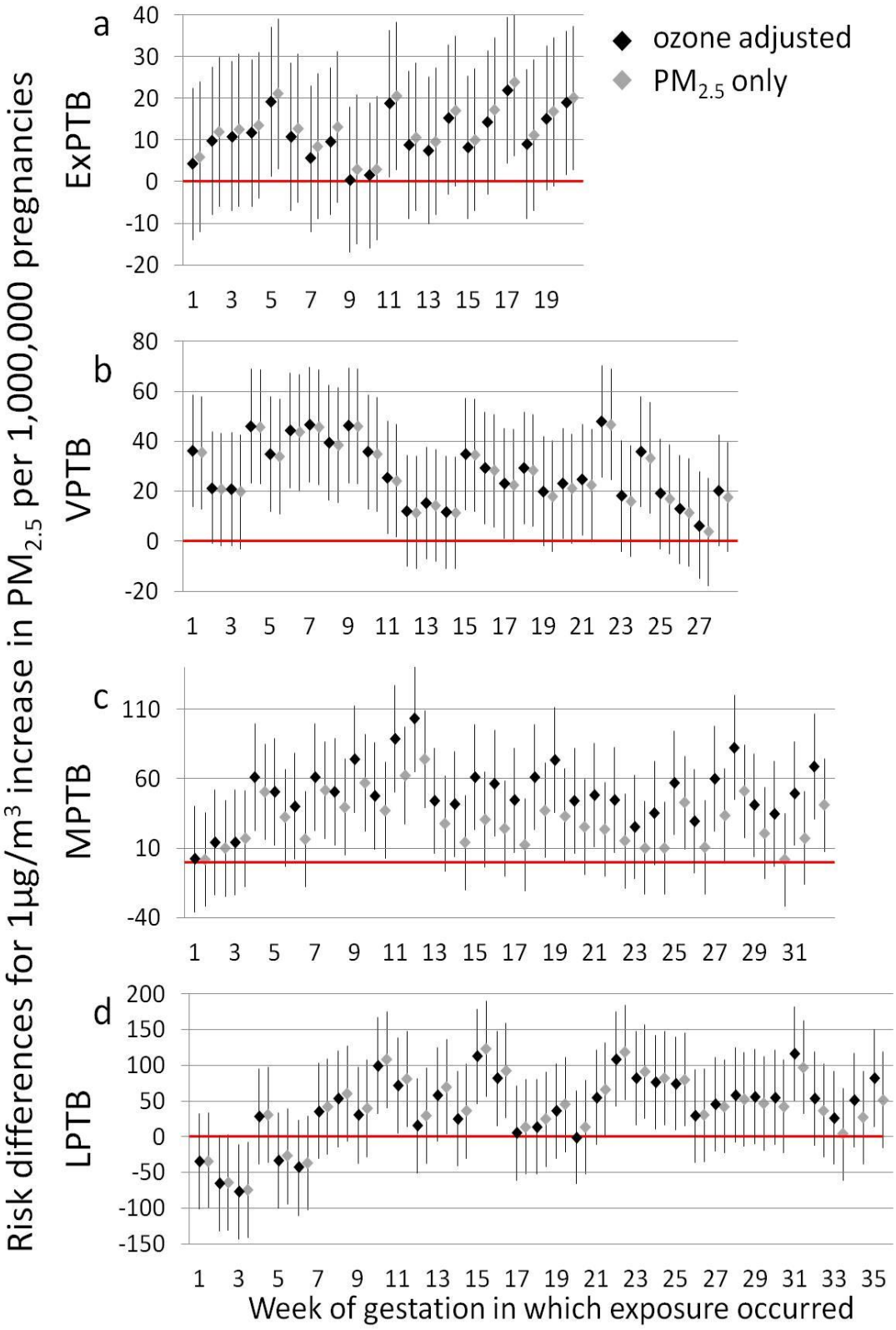

a
ExPTB
ozone adjusted
PM2.5 only
b
VPTB
c
MPTB
d
LPTB
Risk differences for 1µg/m3 increase in PM2.5 per 1,000,000 pregnancies
Week of gestation in which exposure occurred

Figure B.1: Results for $PM_{2.5}$, exposures anchored at conception, with and without adjustment for ozone. Risk differences for preterm birth with 1µg/m3 increases in particulate matter under 2.5 micrometers in aerodynamic diameter (PM2.5) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery (grey diamond) and co-occurring ozone (black diamond). Exposures are anchored at time of conception. a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

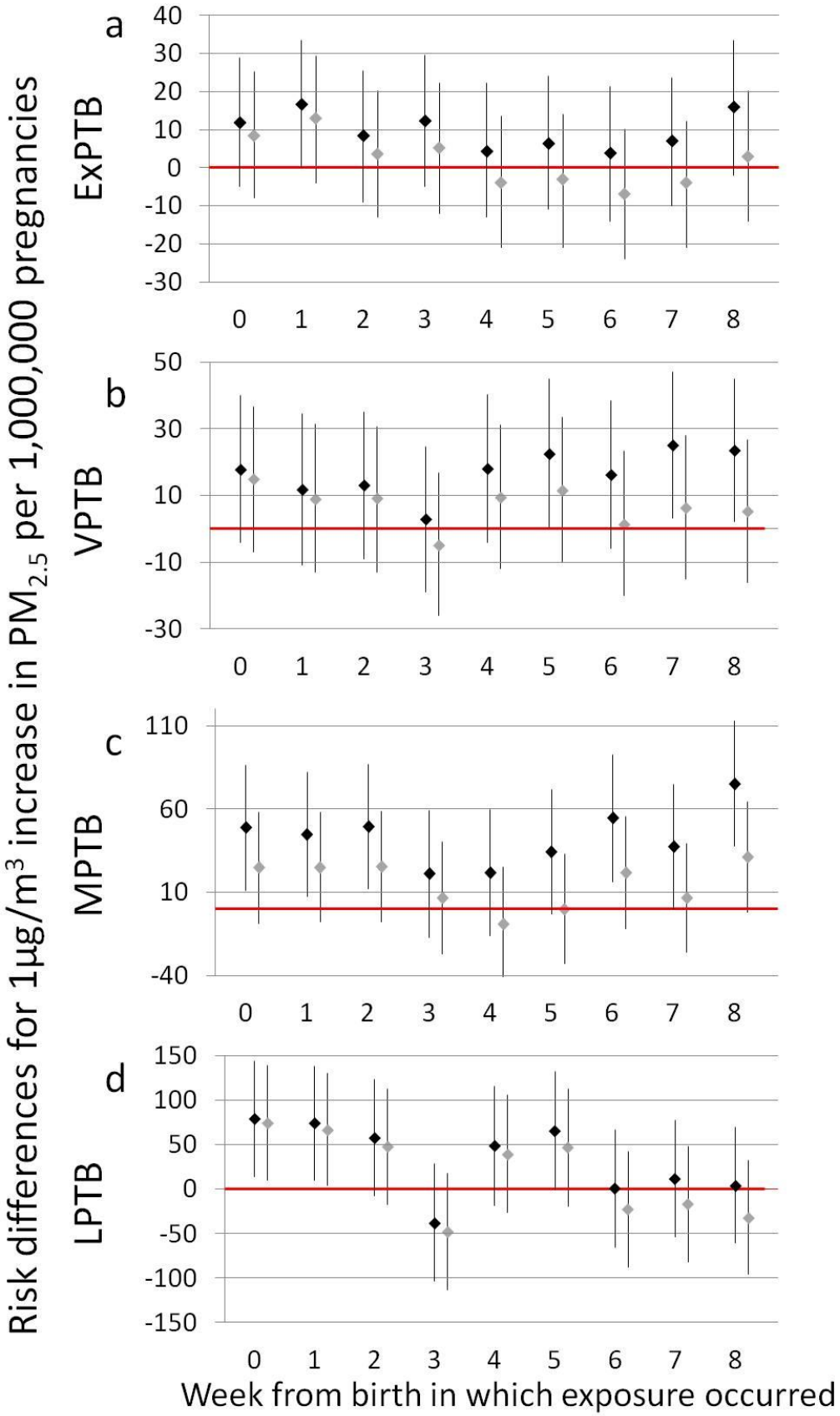

a
ExPTB
40
30
20
10
0
-10
-20
-30
0 1 2 3 4 5 6 7 8
b
VPTB
50
30
10
-10
-30
0 1 2 3 4 5 6 7 8
c
MPTB
110
60
10
-40
0 1 2 3 4 5 6 7 8
d
LPTB
150
100
50
0
-50
-100
-150
0 1 2 3 4 5 6 7 8
Risk differences for 1µg/m3 increase in PM2.5 per 1,000,000 pregnancies
Week from birth in which exposure occurred

Figure B.2: Results for $PM_{2.5}$, lagged exposures, with and without adjustment for ozone. Risk differences for preterm birth with 1µg/m3 increases in particulate matter under 2.5 micrometers in aerodynamic diameter (PM2.5) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery (grey diamond) and co-occurring ozone (black diamond). Exposures are anchored at birth. a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

Table B.1 Results for $PM_{2.5}$, exposures anchored at conception and lagged from birth, adjusted for ozone (as shown in Figures 4.2 and 4.3, and supplemental Figures B.1 and B.2 black diamonds). Risk differences for preterm birth with 1μg/m^3 increases in particulate matter under 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery and co-occurring ozone.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	4.4 (-14, 22.4)	36.2 (13.8, 58.6)	2.3 (-36, 40.2)	-35 (-101, 32.2)
2	9.8 (-8, 27.6)	21.2 (-1, 43.8)	13.9 (-24, 52)	-65 (-132, 1.7)
3	10.8 (-7, 28.8)	20.7 (-2, 43.5)	14.2 (-24, 52.2)	-77 (-144, -11)
4	11.8 (-6, 29.2)	46 (23.2, 68.9)	61.1 (22.6, 99.7)	28.5 (-39, 95.7)
5	19.2 (1.3, 37.1)	34.8 (11.8, 57.8)	50.5 (11.8, 89.3)	-33 (-100, 33.7)
6	10.7 (-7, 28.5)	44.4 (21.3, 67.4)	40.1 (1.8, 78.4)	-43 (-110, 23.1)
7	5.6 (-12, 23)	46.5 (23.5, 69.6)	61 (22.5, 99.5)	35.7 (-31, 102.7)
8	9.6 (-8, 27.4)	39.3 (16.3, 62.4)	50.4 (11.8, 89)	53.3 (-14, 120.4)
9	0.3 (-17, 18)	46.3 (23.3, 69.4)	74 (35.5, 112.5)	30.1 (-37, 97.4)
10	1.5 (-16, 18.9)	35.8 (13, 58.6)	47.8 (9.3, 86.3)	99.5 (32, 167.1)
11	18.8 (1.1, 36.4)	25.4 (2.9, 48)	88.8 (50.1, 127.4)	72.3 (5.5, 139.1)
12	8.9 (-9, 26.6)	12.1 (-10, 34.5)	103.5 (64.7, 142.4)	15.4 (-51, 81.9)
13	7.5 (-10, 25.1)	15.2 (-7, 37.5)	44 (6, 82)	58.6 (-7, 124.4)
14	15.2 (-3, 32.9)	11.6 (-11, 33.9)	41.9 (4.1, 79.8)	25.3 (-41, 91.4)
15	8.2 (-9, 25.3)	34.9 (12.4, 57.3)	61.4 (23.4, 99.3)	113.1 (46.5, 179)
16	14.3 (-3, 31.5)	29.3 (7, 51.7)	56.7 (18.7, 94.7)	81.7 (15.5, 147.8)
17	21.9 (4.4, 39.5)	23.2 (1.1, 45.3)	44.5 (7, 82.1)	5.2 (-61, 71.3)
18	9.1 (-9, 27)	29.4 (7, 51.7)	61.1 (23.3, 99)	13.8 (-52, 79.8)

19	15.1 (-2, 32.6)	19.7 (-2, 41.8)	73.3 (35.3, 111.3)	35.8 (-30, 101.8)
20	18.9 (1.6, 36.1)	23.1 (1.2, 45)	43.9 (6, 81.9)	-1 (-66, 64.7)
21		24.7 (2.4, 46.9)	48.1 (10.6, 85.6)	54.8 (-11, 121)
22		47.9 (25.7, 70.2)	44.5 (6.8, 82.3)	108.8 (42.5, 175)
23		18.1 (-4, 40.3)	25.3 (-12, 62.7)	81.9 (16, 147.8)
24		35.9 (13.7, 58)	35.1 (-2, 72.4)	76.1 (10.3, 142)
25		19.1 (-3, 40.8)	57.1 (19.8, 94.5)	74.3 (9.4, 139.2)
26		12.9 (-9, 34.5)	29.2 (-8, 66.6)	29.1 (-36, 94.4)
27		6.3 (-15, 27.9)	59.9 (22.2, 97.6)	45.3 (-20, 110.9)
28		20.3 (-2, 42.6)	82.5 (45, 120)	58.2 (-8, 124.5)
29			41 (3.9, 78.1)	55.9 (-10, 122.2)
30			34.7 (-3, 72.3)	55.2 (-11, 121.2)
31			49.4 (11.8, 86.9)	115.8 (50.2, 181.5)
32			68.6 (30.8, 106.4)	54 (-12, 119.7)
33				26.3 (-39, 92)
34				51.4 (-14, 116.9)
35				82.2 (14.1, 150.3)
Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	11.8 (-5, 28.9)	17.9 (-4, 40.1)	48.6 (10.8, 86.4)	78.9 (13.6, 144.2)
1	16.6 (0, 33.4)	11.9 (-11, 34.5)	44.8 (7.5, 82.1)	74.3 (10.2, 138.3)
2	8.5 (-9, 25.5)	13.1 (-9, 35)	49.4 (11.9, 86.9)	58.1 (-8, 123.8)
3	12.3 (-5, 29.6)	2.9 (-19, 24.7)	21.1 (-17, 58.9)	-38 (-104, 28.2)
4	4.4 (-13, 22.2)	18.2 (-4, 40.4)	21.7 (-16, 59.5)	48.8 (-18,

				115.9)
5	6.3 (-11, 24)	22.6 (0.3, 44.9)	34.3 (-3, 71.8)	65.8 (-1, 132.7)
6	3.9 (-14, 21.3)	16.2 (-6, 38.4)	54.4 (16.5, 92.3)	1 (-65, 67)
7	7 (-10, 23.7)	25.2 (3.2, 47.2)	37.4 (0.1, 74.7)	11.7 (-54, 77.5)
8	15.9 (-2, 33.4)	23.6 (2.2, 45.1)	75.2 (37.6, 112.8)	4.1 (-61, 69.3)

Table B.2 Results for $PM_{2.5}$, exposures anchored at conception and lagged from birth, not adjusted for ozone (as shown in Figures B.1 and B.2 grey diamonds): Risk differences for preterm birth with $1\mu g/m^3$ increases in particulate matter under 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, and age at delivery.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	5.8 (-12, 23.9)	35.4 (13, 57.8)	1.7 (-32, 35.8)	-34 (-100, 33.1)
2	11.9 (-6, 29.8)	20.7 (-2, 43.3)	9.8 (-25, 44.2)	-64 (-131, 2.3)
3	12.5 (-6, 30.6)	19.8 (-3, 42.6)	16.8 (-18, 51.3)	-74 (-141, -8)
4	13.6 (-4, 31)	45.8 (22.9, 68.7)	50.6 (15.9, 85.2)	30.7 (-36, 97.8)
5	21.1 (3.1, 39.1)	33.8 (10.8, 56.8)	32.1 (-3, 67)	-27 (-94, 39.2)
6	12.7 (-5, 30.6)	43.6 (20.5, 66.7)	16.5 (-18, 50.8)	-37 (-103, 29.4)
7	8.5 (-9, 26)	45.6 (22.5, 68.7)	51.7 (16.9, 86.5)	41.6 (-25, 108.5)
8	13.2 (-5, 31.2)	38.4 (15.4, 61.5)	39.6 (4.8, 74.4)	60.1 (-7, 127.2)
9	3 (-15, 20.9)	45.9 (22.8, 69)	57 (22.3, 91.7)	39.8 (-28, 107.2)
10	3 (-14, 20.4)	34.8 (12, 57.7)	37.3 (2.4, 72.1)	107.9 (40.4, 175.5)
11	20.5 (2.8, 38.2)	24.2 (1.6, 46.8)	62.3 (27.5, 97.2)	81.1 (14.3, 148)
12	10.6 (-7, 28.4)	11.5 (-11, 34)	73.9 (38.8, 108.9)	29.5 (-37, 96)
13	9.5 (-8, 27.3)	14.4 (-8, 36.7)	27.7 (-7, 62)	70 (4.1, 135.8)
14	17 (-1, 34.9)	11.3 (-11, 33.6)	14.1 (-20, 48.1)	36.3 (-30, 102.5)
15	10 (-7, 27.2)	34.5 (12, 57)	30.6 (-4, 64.8)	123.2 (56.6, 189.8)
16	17.2 (0, 34.5)	28.2 (5.7, 50.6)	24.4 (-10, 58.7)	92.5 (26.4, 158.6)
17	23.8 (6.2, 41.4)	22.6 (0.5, 44.7)	12.3 (-21, 45.8)	13.8 (-52, 79.8)
18	11.2 (-7, 29.2)	28.3 (6, 50.7)	37.1 (3, 71.2)	24.4 (-42, 90.4)
19	16.9 (-1, 34.5)	17.9 (-4, 40.1)	33 (-1, 67.2)	45.1 (-21, 111)
20	20.1 (2.8, 37.4)	21.1 (-1, 43)	25.4 (-9, 59.5)	13.4 (-52, 78.9)
21		22.5 (0.3, 44.8)	23.8 (-10, 57.4)	65.8 (0, 131.9)
22		46.7 (24.5, 68.9)	15.3 (-19, 49.2)	118.2 (52, 184.3)
23		16.1 (-6, 38.4)	10.1 (-23, 43.7)	91.4 (25.6, 157.2)
24		33.4 (11.3, 55.6)	9.8 (-23, 43.1)	81.7 (16, 147.4)
25		17 (-5, 38.6)	42.7 (9.3, 76.1)	80.2 (15.5, 144.9)
26		11.4 (-10, 33)	10.8 (-23, 44.2)	30.4 (-35, 95.4)
27		3.9 (-18, 25.4)	33.8 (0.2, 67.4)	42.6 (-22, 107.7)
28		17.6 (-4, 39.7)	50.9 (17.4, 84.5)	52.5 (-13, 118.2)
29			20.6 (-12, 53.6)	47 (-19, 112.7)
30			1.6 (-32, 35.1)	41.9 (-23, 107.3)
31			17.2 (-16, 50.7)	97.4 (32.5, 162.3)
32			41 (7.6, 74.4)	36.9 (-28, 101.8)
33				4 (-61, 68)

34				27 (-38, 91.6)
35				51.7 (-16, 118.9)
Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	8.4 (-8, 25.1)	14.9 (-7, 36.7)	24.6 (-9, 57.9)	74.8 (10.4, 139.2)
1	12.9 (-4, 29.4)	9 (-13, 31.3)	25 (-8, 58)	67 (3.7, 130.3)
2	3.6 (-13, 20.2)	9.1 (-13, 30.7)	25.2 (-8, 58.5)	47.7 (-17, 112.4)
3	5.1 (-12, 22.2)	-5 (-26, 16.8)	6.7 (-27, 40.4)	-48 (-113, 17.8)
4	-4 (-21, 13.5)	9.4 (-12, 31.2)	-9 (-42, 24.9)	39.5 (-26, 105.5)
5	-3 (-21, 14)	11.5 (-10, 33.5)	0 (-33, 32.9)	47 (-19, 112.9)
6	-7 (-24, 10.2)	1.4 (-20, 23.3)	21.8 (-12, 55.4)	-23 (-88, 42.3)
7	-4 (-21, 12.1)	6.4 (-15, 28.1)	6.5 (-26, 39.5)	-17 (-82, 47.8)
8	2.9 (-14, 20.2)	5.4 (-16, 26.6)	31.1 (-2, 64.4)	-32 (-96, 32.7)

Appendix C: $PM_{2.5}$ species supplemental analyses, tables and figures

This appendix contains tables associated with figures shown in Chapter 5, as well as figures discussed but not shown in Chapter 5.

Table C.1 Results for elemental carbon, single-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.1, green diamonds): Risk differences for preterm birth with 0.25μg/m^3 increases in elemental carbon (EC) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	-40 (-123, 43.1)	145.8 (38.1, 253.4)	45.4 (-132, 223.2)	-384 (-695, -72)
2	-45 (-126, 35.9)	106.5 (0.1, 213)	52.6 (-126, 230.8)	-517 (-825, -209)
3	-7 (-92, 78)	86 (-20, 191.7)	87.6 (-91, 266.2)	-495 (-803, -187)
4	-7 (-90, 74.9)	152.8 (45.7, 259.9)	166.2 (-13, 344.9)	-244 (-552, 64.4)
5	0.6 (-85, 86.3)	82.7 (-25, 190.9)	168.9 (-10, 347.5)	-443 (-751, -135)
6	-14 (-96, 68.4)	106.8 (0.1, 213.6)	94.6 (-84, 272.8)	-462 (-767, -157)
7	-16 (-99, 66.5)	116.6 (8.8, 224.5)	144.1 (-34, 322.7)	-239 (-547, 69.3)
8	18.6 (-65, 102.3)	95.8 (-11, 203.1)	202.3 (20.8, 383.9)	-222 (-530, 86)
9	-37 (-120, 45.4)	134.5 (26.8, 242.2)	186 (6.3, 365.6)	-395 (-700, -91)
10	8 (-78, 94.4)	106 (-1, 213.4)	135.6 (-43, 314.4)	-114 (-423, 196.3)
11	54 (-32, 139.6)	55.3 (-51, 162)	275.8 (95.2, 456.4)	-100 (-408, 208)
12	10.2 (-74, 94.5)	47.3 (-58, 152.8)	409.2 (224.9, 593.4)	-215 (-523, 94)
13	6.8 (-76, 89.4)	36 (-68, 140)	323.1 (138.6, 507.6)	-2 (-310, 305.8)
14	1.7 (-82, 85.6)	34.2 (-71, 139.8)	215.3 (32.6, 398)	-168 (-474, 137.4)
15	4.4 (-79, 88.3)	146.5 (37.9, 255.1)	268.8 (86.3, 451.2)	106.5 (-205, 418)
16	23.5 (-59, 105.7)	88.1 (-20, 196.6)	284.7 (102.2, 467.2)	56.1 (-255, 366.9)
17	39.7 (-47, 126.1)	81.8 (-27, 191.1)	275 (93.8, 456.2)	-278 (-589, 32)
18	-13 (-99, 73)	93.9 (-15, 203.1)	254.7 (71.6, 437.9)	-229 (-539, 79.6)
19	-12 (-96, 71.8)	99.1 (-11, 209.4)	257.1 (74.2, 440.1)	-9 (-320, 302.2)
20	2.1 (-84, 87.8)	89.2 (-20, 198.3)	232.9 (51.9, 413.9)	-98 (-407, 211.8)
21		85.5 (-24, 195.4)	170.8 (-10, 351.3)	-66 (-379, 247.3)
22		165.4 (55.6, 275.1)	184.7 (2.4, 367.1)	-24 (-336, 288.2)
23		17.7 (-90, 125.1)	145.1 (-38, 328)	-11 (-322, 300)
24		111.6 (2.5, 220.7)	140.6 (-41, 322.5)	-53 (-366, 260.3)
25		64.9 (-44, 173.4)	134 (-47, 315.3)	-157 (-467,

				152.8)
26		107.7 (-3, 218.7)	49.1 (-134, 232.3)	-305 (-620, 10.7)
27		69.2 (-41, 179.1)	159.5 (-26, 345.3)	-278 (-592, 36.4)
28		115.7 (4.8, 226.6)	294 (109.7, 478.4)	-252 (-571, 67.2)
29			69.9 (-113, 253.1)	-292 (-612, 28.8)
30			88.4 (-96, 272.7)	-319 (-636, -3)
31			123.3 (-60, 306.8)	-88 (-406, 229.8)
32			199.6 (14.3, 384.8)	-269 (-586, 48.8)
33				-320 (-638, -2)
34				-216 (-532, 100.4)
35				-337 (-658, -17)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	9.3 (-81, 99.8)	141.1 (29.5, 252.8)	153.4 (-29, 335.8)	-157 (-472, 158.3)
1	25.8 (-58, 109.8)	91.8 (-20, 203.3)	222.9 (40.8, 405)	-178 (-488, 132)
2	-29 (-114, 56.5)	145.2 (34.3, 256.1)	228.2 (45.1, 411.3)	-7 (-324, 309.8)
3	5 (-84, 94)	108.6 (-3, 220.2)	112.1 (-73, 297.1)	-323 (-641, -5)
4	-29 (-119, 61.7)	122.7 (10.8, 234.5)	77.4 (-105, 260)	19.2 (-301, 339.4)
5	-30 (-120, 60.2)	81.2 (-32, 194.3)	180.4 (-4, 364.9)	-173 (-491, 145.9)
6	-75 (-161, 10.5)	69 (-41, 179.5)	198.5 (13.5, 383.5)	-353 (-672, -35)
7	-83 (-168, 1.2)	45.9 (-65, 157.1)	122 (-65, 309.5)	-331 (-650, -13)
8	-42 (-130, 46.6)	59.1 (-51, 169.3)	162.6 (-23, 348.2)	-487 (-803, -172)

Table C.2 Results for elemental carbon, multi-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.1, purple circles): Risk differences for preterm birth with 0.25μg/m^3 increases in elemental carbon (EC) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, co-occurring ozone, organic carbons, nitrates, and sulfates.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	-21 (-146, 104.5)	208.1 (47.4, 368.7)	275.6 (9.9, 541.4)	285.2 (-174, 744.5)
2	-37 (-159, 85.7)	206.7 (46.5, 366.9)	335.8 (70, 601.6)	42.9 (-415, 500.7)
3	11.1 (-119, 140.9)	195.9 (36.2, 355.6)	385 (115.3, 654.7)	266.6 (-191, 723.8)
4	23.2 (-102, 148.6)	196 (34.6, 357.3)	372 (103.5, 640.5)	396.9 (-61, 855)
5	16.1 (-111, 143.6)	109.3 (-53, 271.4)	303.9 (37.2, 570.7)	363.1 (-93, 819.3)
6	3.5 (-119, 126.4)	112 (-47, 271.4)	268.3 (0.2, 536.5)	308.7 (-145, 761.9)
7	-8 (-133, 116.6)	123.9 (-36, 283.9)	318.6 (53.3, 583.9)	287.6 (-168, 743.3)
8	37.5 (-89, 163.8)	103.5 (-56, 263.4)	417.2 (146.4, 688.1)	284.2 (-173, 741.4)
9	-16 (-139, 108)	132.7 (-27, 292.5)	374.8 (105.6, 644)	129.3 (-322, 580.9)
10	43.6 (-82, 169.5)	117.8 (-44, 279.9)	299.9 (29.9, 570)	271.9 (-186, 730.1)
11	72.4 (-55, 199.7)	64.9 (-97, 226.9)	297.3 (25.7, 569)	340.5 (-115, 795.6)
12	3.7 (-121, 128.9)	89.7 (-70, 249.5)	437.2 (163.6, 710.8)	449 (-7, 905.3)
13	-41 (-170, 88.3)	94.7 (-63, 252.4)	467.8 (193.9, 741.7)	559.2 (100.6, 1017.8)
14	-65 (-193, 63.9)	111 (-49, 271.2)	348.6 (76.6, 620.5)	438.2 (-19, 894.9)
15	-39 (-169, 90.1)	200.6 (37.4, 363.8)	294.1 (23.6, 564.7)	431.9 (-31, 895.3)
16	-33 (-159, 93.6)	140 (-24, 304.4)	379.6 (107.8, 651.4)	561.6 (99.1, 1024.2)
17	-10 (-146, 125.3)	144.4 (-18, 307.1)	373.4 (104.6, 642.2)	295.9 (-166, 757.7)
18	-75 (-203, 53.6)	144.9 (-18, 307.6)	385.5 (113.9, 657)	212 (-248, 671.9)
19	-93 (-221, 34.3)	198.5 (34.6, 362.5)	278.1 (6.6, 549.6)	537.9 (75, 1000.8)
20	-56 (-185, 74)	124.1 (-41, 289.3)	280.3 (9.5, 551)	514 (53.2, 974.8)

21		109.7 (-54, 273.8)	155.2 (-114, 424.7)	346.7 (-117, 810.3)
22		180.7 (17.5, 344)	161.8 (-110, 433.3)	296.8 (-166, 759.2)
23		37.7 (-124, 198.9)	161.3 (-111, 433.8)	312.4 (-149, 774.1)
24		54.3 (-108, 216.4)	234 (-38, 506)	178.2 (-285, 641.9)
25		52 (-108, 211.9)	80.3 (-190, 350.7)	-39 (-498, 419.6)
26		178.8 (17.1, 340.6)	61.9 (-209, 333)	-246 (-709, 217)
27		173.8 (11, 336.6)	66.1 (-208, 340.2)	-250 (-715, 216.1)
28		180.4 (17.1, 343.7)	88.5 (-184, 361.3)	-120 (-590, 350.4)
29			-56 (-327, 215)	-205 (-674, 263.3)
30			45.8 (-226, 317.9)	-305 (-769, 158.7)
31			91.7 (-179, 362.2)	-172 (-637, 292.9)
32			67.8 (-204, 339.9)	-314 (-778, 151)
33				-244 (-708, 219.6)
34				-122 (-584, 340.6)
35				-342 (-809, 124.7)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	-36 (-167, 94.9)	200.2 (36.7, 363.7)	65.3 (-202, 332.7)	-446 (-907, 15.6)
1	-22 (-148, 104)	199.6 (38.4, 360.7)	266.2 (-4, 536.6)	-248 (-704, 207.9)
2	-38 (-165, 89.7)	287.8 (126.5, 449.1)	187.2 (-81, 455.6)	-25 (-487, 437.7)
3	-60 (-192, 71.5)	265.2 (102.2, 428.1)	275.1 (4.7, 545.5)	3.9 (-459, 466.4)
4	-129 (-258, 0.7)	188.8 (26.8, 350.8)	129.6 (-138, 396.9)	184.9 (-281, 650.3)
5		73.1 (-88, 234)	222.8 (-47, 492.7)	216.5 (-247, 679.8)
6		78.9 (-82, 239.6)	141.1 (-130, 412.7)	88.1 (-376, 552.2)
7		-31 (-193, 131.1)	164.5 (-110, 438.6)	187 (-278, 652.1)
8		-9 (-170, 151.9)	20.8 (-251, 293)	-97 (-560, 366.6)

Table C.3 Results for organic carbons, single-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.2, green diamonds): Risk differences for preterm birth with 1μg/m^3 increases in organic carbons (OC) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	-25 (-130, 80.4)	25.5 (-108, 159.1)	-248 (-473, -23)	-1043 (-1440, -646)
2	-45 (-149, 59.1)	-60 (-190, 69.9)	-241 (-466, -17)	-1145 (-1536, -754)
3	-20 (-124, 84)	-47 (-178, 84.7)	-325 (-545, -105)	-1083 (-1473, -694)
4	-6 (-104, 91.6)	40.5 (-91, 172.2)	-146 (-370, 78.2)	-885 (-1275, -496)
5	-5 (-107, 97.9)	-18 (-153, 115.8)	-122 (-347, 102.4)	-1146 (-1535, -756)
6	-26 (-126, 74.3)	19.8 (-116, 155.5)	-198 (-423, 27)	-1215 (-1602, -829)
7	0.3 (-101, 101.5)	9.6 (-124, 143.5)	-165 (-389, 58.5)	-871 (-1263, -479)
8	8.6 (-92, 108.9)	6 (-129, 141.4)	-104 (-329, 120.7)	-897 (-1286, -508)
9	-34 (-137, 68.5)	28.3 (-102, 158.2)	-139 (-361, 82.5)	-1023 (-1411, -636)
10	7.2 (-98, 112.7)	13.1 (-122, 147.7)	-157 (-382, 68.5)	-730 (-1122, -338)
11	44.1 (-59, 146.7)	-69 (-203, 64.8)	29.9 (-195, 254.4)	-670 (-1061, -280)
12	0.6 (-104, 105.4)	-49 (-185, 86.3)	167.1 (-63, 397.4)	-960 (-1347, -572)
13	9.9 (-93, 112.8)	-54 (-187, 78.9)	79.5 (-150, 308.7)	-725 (-1112, -338)
14	3 (-99, 104.6)	-79 (-210, 51.8)	-73 (-300, 153.8)	-986 (-1373, -599)
15	-12 (-113, 90.4)	36.4 (-98, 170.5)	10 (-217, 236.9)	-586 (-979, -193)
16	31.1 (-68, 130.8)	-49 (-182, 84.2)	53.5 (-173, 280.1)	-649 (-1042, -257)
17	32.1 (-69, 133.7)	-41 (-173, 91.3)	79.5 (-149, 308.3)	-1101 (-1493, -710)
18	-31 (-134, 72.4)	-11 (-144, 121.8)	-27 (-256, 202.3)	-992 (-1384, -600)
19	-12 (-116, 91.9)	-33 (-167, 101.4)	12.2 (-217, 240.9)	-823 (-1216, -430)
20	-31 (-135, 73.9)	-19 (-151, 113.6)	-25 (-253, 202.3)	-971 (-1362, -581)
21		-1 (-137, 134.3)	-48 (-275, 178.3)	-888 (-1282, -495)

22		68.5 (-69, 205.5)	-20 (-249, 208.4)	-840 (-1236, -444)
23		-80 (-218, 57.5)	-61 (-291, 169.4)	-835 (-1230, -439)
24		50.6 (-86, 187.2)	-167 (-394, 60.2)	-812 (-1208, -415)
25		16.3 (-122, 154.5)	-84 (-314, 146.5)	-778 (-1174, -383)
26		10.2 (-130, 150.1)	-208 (-441, 24.9)	-867 (-1274, -459)
27		-23 (-164, 118.1)	-12 (-251, 226.3)	-846 (-1251, -441)
28		11.6 (-130, 152.8)	237.3 (0.7, 473.9)	-970 (-1381, -558)
29			-90 (-329, 149.2)	-845 (-1261, -429)
30			-101 (-341, 139.4)	-757 (-1172, -342)
31			-82 (-322, 157.5)	-484 (-902, -67)
32			98.1 (-143, 339.1)	-741 (-1157, -325)
33				-914 (-1330, -498)
34				-698 (-1113, -283)
35				-809 (-1232, -386)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	119.9 (6, 233.7)	158.2 (14.6, 301.9)	217.2 (-23, 457.6)	-151 (-566, 263.8)
1	182.1 (72.8, 291.4)	90.9 (-52, 234)	170.5 (-66, 407)	-222 (-628, 183.9)
2	117.1 (7.3, 227)	182.3 (37.2, 327.4)	276.4 (35.9, 516.9)	-33 (-449, 383.9)
3	173.2 (60, 286.4)	124.1 (-21, 269.1)	74.1 (-169, 316.7)	-521 (-940, -103)
4	146.6 (30.5, 262.7)	190.7 (45.1, 336.2)	122.8 (-117, 362.8)	-9 (-430, 411.6)
5	150.6 (33.9, 267.2)	203.8 (55.9, 351.8)	178 (-64, 420)	-370 (-791, 51.3)
6	122 (8.5, 235.6)	158.8 (12.9, 304.6)	273.6 (31.6, 515.7)	-573 (-991, -154)
7	105.7 (-6, 217.2)	168 (21.1, 315)	155.8 (-88, 399.8)	-715 (-1131, -299)
8	180.4 (67.1, 293.6)	201.6 (56.1, 347.1)	285.8 (43.6, 528)	-894 (-1305, -484)

Table C.4 Results for organic carbons, multi-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.2, purple circles): Risk differences for preterm birth with 1μg/m^3 increases in organic carbons (OC) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, co-occurring ozone, elemental carbon, nitrates, and sulfates.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	-71 (-231, 88.9)	-260 (-464, -57)	-555 (-901, -210)	-1744 (-2341, -1146)
2	-102 (-259, 55.3)	-313 (-514, -113)	-688 (-1031, -345)	-1467 (-2061, -874)
3	-111 (-271, 47.7)	-312 (-512, -113)	-799 (-1140, -459)	-1677 (-2266, -1088)
4	-110 (-261, 40.2)	-279 (-479, -79)	-759 (-1104, -414)	-1884 (-2472, -1296)
5	-129 (-280, 22.9)	-242 (-447, -37)	-584 (-927, -242)	-2005 (-2592, -1418)
6	-100 (-252, 51.3)	-237 (-441, -33)	-637 (-980, -294)	-1955 (-2541, -1369)
7	-36 (-189, 116.7)	-255 (-458, -53)	-714 (-1054, -375)	-1735 (-2325, -1145)
8	-71 (-224, 82.5)	-219 (-422, -16)	-681 (-1025, -337)	-1836 (-2425, -1246)
9	-58 (-214, 98.4)	-232 (-430, -33)	-789 (-1130, -447)	-1816 (-2403, -1229)
10	-41 (-198, 116.6)	-193 (-399, 12.4)	-627 (-976, -279)	-1729 (-2320, -1139)
11	-82 (-238, 73.7)	-205 (-414, 4)	-498 (-844, -152)	-1593 (-2181, -1005)
12	-34 (-191, 122.9)	-154 (-364, 55.5)	-473 (-822, -124)	-1856 (-2437, -1274)
13	42 (-118, 202)	-205 (-409, 0)	-372 (-718, -26)	-1725 (-2310, -1140)
14	22.8 (-132, 177.2)	-222 (-425, -19)	-470 (-813, -128)	-1862 (-2451, -1274)
15	17.6 (-140, 175.1)	-244 (-448, -40)	-346 (-688, -5)	-1567 (-2160, -974)
16	34.2 (-120, 188.3)	-261 (-465, -57)	-400 (-742, -59)	-1683 (-2276, -1089)
17	-14 (-174, 146.2)	-240 (-442, -38)	-305 (-650, 38.7)	-1731 (-2321, -1141)
18	16.5 (-139, 171.7)	-253 (-454, -53)	-522 (-866, -178)	-1498 (-2089, -907)
19	23.3 (-136, 182.6)	-273 (-474, -73)	-420 (-764, -76)	-1643 (-2237, -1050)
20	-35 (-196, 125.5)	-188 (-390, 14.6)	-333 (-678, 12.8)	-1676 (-2267, -1085)
21		-171 (-372, 30.5)	-274 (-618, 69)	-1639 (-2232, -1047)
22		-226 (-431, -20)	-220 (-564, 124.6)	-1741 (-2338, -

				1145)
23		-193 (-400, 13.4)	-210 (-556, 135.6)	-1582 (-2182, -983)
24		-76 (-281, 130)	-469 (-812, -126)	-1411 (-2007, -814)
25		-73 (-279, 132.3)	-281 (-627, 64)	-1209 (-1807, -612)
26		-166 (-371, 39.1)	-344 (-689, 1)	-931 (-1534, -327)
27		-210 (-419, -2)	-202 (-554, 149.2)	-968 (-1572, -364)
28		-200 (-409, 8.6)	16.1 (-335, 367)	-1268 (-1880, -657)
29			-92 (-446, 261.6)	-1073 (-1687, -459)
30			-205 (-563, 152.3)	-895 (-1511, -279)
31			-296 (-652, 60.7)	-877 (-1494, -259)
32			-109 (-467, 248.3)	-793 (-1407, -180)
33				-953 (-1569, -337)
34				-953 (-1570, -336)
35				-1047 (-1670, -424)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	80.1 (-85, 244.8)	-72 (-286, 141.8)	6.6 (-352, 365.2)	-83 (-699, 533.8)
1	110.4 (-56, 277.2)	-162 (-374, 49.2)	-201 (-559, 156.7)	-457 (-1068, 153.3)
2	35.2 (-130, 200.1)	-153 (-367, 61.2)	-17 (-377, 343.9)	-330 (-949, 288.1)
3	142 (-24, 308.4)	-163 (-376, 51)	-338 (-698, 22.7)	-724 (-1342, -106)
4	227.8 (61.7, 394)	-63 (-278, 151)	-125 (-481, 231.5)	-556 (-1178, 66.8)
5		12.1 (-202, 226)	-124 (-482, 234.3)	-1279 (-1904, -655)
6		0.9 (-213, 215.1)	-29 (-389, 330.6)	-1118 (-1739, -498)
7		80.8 (-132, 293.5)	-173 (-532, 184.8)	-1367 (-1984, -751)
8		113.1 (-99, 325.4)	-22 (-379, 333.6)	-1283 (-1895, -670)

Table C.5 Results for NO_3, single-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.3, green diamonds): Risk differences for preterm birth with $1\mu g/m^3$ increases in nitrates (NO_3) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	101.8 (25.4, 178.2)	37.3 (-59, 133.6)	-92 (-257, 72.9)	55.9 (-231, 342.5)
2	81.5 (5.6, 157.4)	-27 (-121, 66.8)	51.3 (-112, 214.4)	-176 (-459, 106.5)
3	79.1 (1.6, 156.6)	45.6 (-52, 143.6)	-108 (-271, 55.1)	178.3 (-107, 463.3)
4	115.6 (40.5, 190.6)	76.7 (-21, 174.6)	126.5 (-36, 289)	318.2 (35.7, 600.7)
5	110.1 (34.6, 185.7)	40.2 (-57, 137.4)	-37 (-198, 125)	233.8 (-48, 516.1)
6	66.6 (-8, 141.2)	67.1 (-30, 164.7)	-16 (-179, 145.9)	44.4 (-235, 323.5)
7	69.3 (-5, 143.2)	50 (-45, 145.3)	39 (-121, 198.8)	135.7 (-145, 416)
8	57.3 (-14, 128.5)	41.1 (-56, 138.2)	49.6 (-112, 210.9)	133.3 (-145, 411.3)
9	55.9 (-18, 130)	25.7 (-71, 122.8)	116.6 (-43, 276.2)	173.3 (-107, 453.4)
10	53.2 (-19, 125.6)	16.9 (-79, 112.8)	18.5 (-143, 180.3)	201 (-81, 482.8)
11	84 (9.7, 158.3)	-69 (-163, 26)	21.3 (-140, 182.5)	193.8 (-85, 472.8)
12	11.8 (-61, 85.1)	-43 (-137, 50)	57.9 (-103, 218.9)	2.9 (-272, 278)
13	-48 (-118, 23.2)	16.9 (-76, 109.6)	-79 (-237, 78.3)	35 (-238, 308.2)
14	-38 (-112, 36.3)	-17 (-111, 76.2)	-143 (-299, 13.7)	-105 (-379, 169.4)
15	-67 (-139, 4.9)	47.4 (-47, 141.4)	-201 (-357, -46)	-86 (-362, 189.9)
16	-25 (-96, 46.8)	-26 (-120, 67.5)	-46 (-205, 113.1)	21 (-255, 297.3)
17	-4 (-78, 69.1)	-19 (-111, 73.6)	-49 (-207, 109.3)	-339 (-614, -64)
18	-83 (-157, -10)	38.5 (-55, 131.6)	-49 (-208, 110.1)	-414 (-690, -138)
19	-50 (-123, 22.8)	-1 (-97, 94.1)	-80 (-238, 77.2)	-278 (-554, -2)
20	-53 (-124, 18.2)	-37 (-130, 55.2)	-189 (-349, -29)	-415 (-690, -139)
21		-14 (-111, 82.6)	-186 (-343, -28)	-341 (-617, -65)
22		56 (-38, 150.4)	-213 (-372, -55)	-232 (-509, 44.5)

23		-41 (-136, 54.5)	-243 (-399, -86)	-374 (-650, -98)
24		-37 (-131, 56.1)	-212 (-372, -53)	-439 (-717, -161)
25		-23 (-118, 70.6)	-205 (-365, -45)	-354 (-631, -77)
26		-21 (-116, 73.9)	-279 (-439, -118)	-562 (-843, -281)
27		33.9 (-63, 130.9)	-187 (-347, -27)	-518 (-799, -237)
28		7 (-89, 102.9)	-90 (-252, 71.5)	-543 (-825, -261)
29			-293 (-454, -131)	-366 (-651, -81)
30			-233 (-395, -70)	-284 (-568, 0.5)
31			-163 (-324, -1)	-141 (-425, 143.9)
32			-75 (-238, 88.6)	-471 (-754, -188)
33				-603 (-884, -323)
34				-295 (-573, -17)
35				-202 (-491, 86.7)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	184.4 (111.4, 257.4)	189.7 (96.2, 283.2)	191.4 (31.6, 351.3)	-28 (-305, 249.4)
1	265.2 (192.5, 337.9)	215.2 (119.7, 310.8)	182 (23.6, 340.5)	271.6 (-3, 546.5)
2	284.7 (210, 359.4)	330.9 (234.9, 426.8)	225.5 (67.8, 383.2)	254.1 (-26, 533.9)
3	248.3 (173.9, 322.7)	275.3 (180, 370.7)	336.6 (175.2, 497.9)	201.6 (-80, 482.8)
4	195.6 (120.2, 271.1)	279.6 (183.4, 375.9)	278.1 (117.9, 438.3)	532.2 (251.7, 812.7)
5	162.2 (88, 236.4)	313.9 (216.1, 411.7)	200.2 (39.7, 360.7)	844.6 (562.4, 1126.8)
6	123.7 (48.7, 198.7)	253.9 (158.2, 349.7)	282.4 (121.3, 443.5)	570.5 (287.9, 853.1)
7	161.1 (85.2, 237.1)	225 (128, 322)	318.4 (156.8, 479.9)	445 (163, 727.1)
8	89.8 (11.9, 167.8)	245 (146, 343.9)	362.1 (198.3, 525.9)	232.1 (-51, 515.4)

Table C.6 Results for NO_3, multi-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.3, purple circles): Risk differences for preterm birth with 1μg/m^3 increases in nitrates (NO_3) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, co-occurring ozone, elemental carbon, organic carbons, and sulfates.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	121 (34.2, 207.8)	98.8 (-9, 207)	37.1 (-148, 221.9)	524.6 (204.6, 844.7)
2	112.9 (28.3, 197.5)	43.7 (-62, 149.1)	211.1 (28.8, 393.4)	221.9 (-93, 537.2)
3	109.8 (24.2, 195.5)	110.6 (2, 219.3)	80.7 (-101, 262.6)	593.5 (276.5, 910.4)
4	141.7 (58.2, 225.2)	143.5 (35.4, 251.6)	311.7 (130.4, 493)	801.1 (487.2, 1114.9)
5	144.8 (61.1, 228.5)	96.9 (-11, 204.8)	109.2 (-70, 288.3)	739.1 (426.2, 1052)
6	91.9 (9, 174.8)	129.2 (22.3, 236.2)	146 (-34, 325.6)	544.5 (235.1, 853.9)
7	79.3 (-3, 161.2)	114.4 (9, 219.9)	217.7 (39.9, 395.5)	599.1 (288.1, 910.1)
8	73.5 (-5, 152.5)	99.3 (-8, 206.3)	199.9 (19.8, 380)	637.2 (328.1, 946.4)
9	71 (-12, 153.9)	80.1 (-27, 187.2)	308.8 (131.1, 486.6)	669.8 (358.3, 981.4)
10	56.9 (-24, 137.5)	64.4 (-41, 170.3)	167.8 (-12, 347.5)	672.7 (360.2, 985.2)
11	100.2 (17.6, 182.8)	-11 (-115, 92.8)	142.5 (-36, 321.4)	605.7 (296.5, 914.8)
12	21.8 (-59, 102.5)	-6 (-108, 96.1)	160.3 (-18, 338.4)	457.1 (152.7, 761.5)
13	-52 (-130, 25.7)	66.1 (-35, 167.3)	-20 (-194, 154.1)	450.5 (148.6, 752.4)
14	-34 (-115, 45.9)	31.4 (-71, 134.1)	-42 (-214, 130.7)	357.1 (54.5, 659.7)
15	-64 (-142, 14.7)	99.3 (-3, 201.8)	-127 (-299, 44.2)	310.1 (5.9, 614.4)
16	-25 (-105, 53.6)	33.4 (-69, 136.2)	32.6 (-142, 207.2)	424.4 (119.2, 729.5)
17	3.8 (-77, 85)	32.3 (-70, 134.5)	2.8 (-172, 177.6)	93.3 (-210, 396.4)
18	-80 (-161, 0)	94.3 (-9, 197.2)	62.9 (-112, 238.1)	-27 (-331, 276.9)
19	-47 (-127, 32.6)	51.9 (-53, 156.4)	18.5 (-156, 192.9)	118.8 (-186, 423.6)
20	-31 (-111, 48.4)	7.8 (-94, 109.9)	-121 (-297, 54.9)	-6 (-309, 298.2)
21		26.1 (-80, 132.4)	-112 (-287, 62.1)	78 (-227, 383.4)
22		109.8 (5.4, 214.2)	-158 (-333, 16.9)	233.2 (-73,

				539.6)
23		16 (-87, 119.2)	-191 (-364, -18)	50.3 (-256, 356.2)
24		-9 (-112, 94.1)	-102 (-278, 72.8)	-54 (-362, 252.8)
25		-1 (-105, 102.1)	-117 (-293, 57.9)	5.9 (-301, 312.4)
26		10.7 (-93, 114.4)	-176 (-352, 0.5)	-266 (-575, 43.4)
27		73.8 (-32, 179.3)	-113 (-290, 63.1)	-212 (-521, 97.5)
28		46.3 (-59, 151.7)	-66 (-243, 111)	-174 (-484, 136.9)
29			-238 (-415, -61)	-37 (-350, 276.5)
30			-166 (-345, 12.2)	10.2 (-302, 322.9)
31			-71 (-248, 105.9)	152.5 (-160, 465.5)
32			-28 (-207, 151.7)	-197 (-507, 113.5)
33				-297 (-606, 11.5)
34				2.5 (-304, 309.2)
35				151.5 (-167, 469.7)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	164.9 (86.2, 243.6)	186.5 (83.7, 289.3)	194.9 (20, 369.9)	76.9 (-227, 381)
1	238.1 (157.7, 318.4)	233.1 (127.7, 338.4)	215.9 (41.3, 390.5)	441.3 (138.4, 744.2)
2	272.6 (191.2, 354.1)	333.9 (228.4, 439.4)	221.7 (47.2, 396.3)	361.7 (53.8, 669.7)
3	213.6 (132.8, 294.3)	281.5 (177.6, 385.4)	392 (214.4, 569.5)	371.6 (61.7, 681.4)
4	149.2 (67.3, 231.1)	271.7 (167, 376.3)	296.9 (120.8, 473)	660.4 (351.1, 969.7)
5		300 (194, 405.9)	213.6 (37.4, 389.7)	1158.5 (846.5, 1470.4)
6		244.5 (140, 348.9)	287.5 (110.3, 464.7)	837.5 (525.8, 1149.3)
7		210.2 (105, 315.4)	348.5 (171.7, 525.3)	768 (457.3, 1078.7)
8		218.9 (111.1, 326.7)	382.3 (203, 561.7)	565 (252.7, 877.3)

Table C.7 Results for SO_4, single-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.4, green diamonds). Risk differences for preterm birth with $1\mu g/m^3$ increases in sulfates (SO_4) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	-4 (-33, 24.7)	62.5 (25.9, 99.1)	46 (-16, 108.1)	56.1 (-53, 165)
2	13.6 (-15, 42.3)	51.5 (14.4, 88.5)	45.5 (-17, 108)	31.8 (-77, 140.8)
3	11 (-18, 39.9)	38.2 (1.7, 74.7)	83.2 (20.1, 146.4)	-51 (-160, 57.3)
4	3.4 (-24, 31.2)	74.7 (37.5, 111.8)	121.9 (58.5, 185.3)	123.6 (13.5, 233.7)
5	19.6 (-9, 48.1)	66.5 (29.7, 103.2)	122.8 (59.7, 186)	32.5 (-76, 141.2)
6	10.8 (-17, 38.8)	78.6 (41.7, 115.5)	107.3 (44.9, 169.6)	49.9 (-59, 158.4)
7	-3 (-30, 25)	85.3 (48, 122.7)	135.5 (72.6, 198.4)	164.1 (55.2, 273)
8	6.2 (-22, 34.8)	74.8 (37.7, 112)	107.6 (45.3, 170)	203.7 (94.6, 312.8)
9	-6 (-34, 22.6)	83.6 (46.6, 120.7)	144.7 (82.3, 207.1)	163.9 (54.5, 273.2)
10	-11 (-39, 16)	66.6 (30.2, 103)	111.2 (49.2, 173.3)	265.1 (155.8, 374.3)
11	14.6 (-13, 42.7)	68.5 (32.3, 104.7)	176.2 (113.9, 238.6)	200.8 (92.8, 308.8)
12	14.2 (-14, 42.2)	33.2 (-2, 68.8)	186.5 (123.9, 249)	139.2 (31.6, 246.9)
13	20.6 (-8, 49.3)	29.4 (-6, 64.8)	89.9 (29, 150.8)	187.2 (80.2, 294.1)
14	38.2 (9.5, 66.9)	28.8 (-7, 65)	115.4 (54.2, 176.7)	187.2 (79, 295.4)
15	29.8 (1.5, 58)	58.7 (22.5, 94.8)	155.3 (93.5, 217)	314.4 (206, 422.9)
16	29.6 (1.4, 57.8)	66.5 (30, 102.9)	116.9 (55.3, 178.5)	227 (119.2, 334.7)
17	42.8 (14.4, 71.2)	51.2 (15.3, 87.1)	87.9 (27.4, 148.4)	176.9 (69.5, 284.3)
18	37.1 (8.2, 65.9)	54.4 (18.2, 90.6)	131.8 (70.4, 193.1)	197.4 (89.8, 305)
19	44.6 (15.9, 73.3)	41.9 (6.3, 77.4)	166.4 (104.5, 228.2)	199.9 (92, 307.9)
20	53.7 (25.1, 82.2)	53.3 (17.4, 89.3)	130.4 (68.5, 192.4)	169.3 (61.3, 277.3)

21		53 (16.7, 89.3)	138.7 (76.9, 200.5)	273 (164.2, 381.7)
22		82 (45.9, 118.1)	132.5 (70.8, 194.3)	365.4 (256.4, 474.5)
23		54.2 (18, 90.3)	103.5 (42.3, 164.6)	320 (211.9, 428.1)
24		72.5 (36.7, 108.4)	129.2 (68.9, 189.4)	317 (210.4, 423.6)
25		40.8 (6, 75.6)	159.8 (99.2, 220.3)	303.3 (197.9, 408.6)
26		28.1 (-6, 62.5)	130.3 (70.1, 190.5)	249.6 (144.8, 354.5)
27		10.1 (-24, 44.2)	155.6 (95, 216.2)	266 (160.6, 371.3)
28		37.4 (2.3, 72.6)	161.3 (101.3, 221.4)	300.2 (194, 406.4)
29			143.1 (84.2, 201.9)	251.9 (146.6, 357.2)
30			116.9 (57.6, 176.3)	230 (125.6, 334.5)
31			133.5 (74.1, 192.9)	309.7 (206, 413.4)
32			141.3 (82.1, 200.6)	260.9 (157.6, 364.1)
33				239.9 (136.3, 343.5)
34				217.2 (113.8, 320.6)
35				278.9 (171.6, 386.2)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	-13 (-39, 12.5)	-10 (-44, 25.3)	49.6 (-10, 109.2)	179.9 (76.5, 283.4)
1	-18 (-44, 8.5)	-17 (-52, 18)	45.6 (-13, 104.5)	126.6 (25.1, 228)
2	-29 (-55, -3)	-40 (-74, -7)	38.6 (-20, 97.4)	80.7 (-22, 183.9)
3	-22 (-48, 3.4)	-45 (-78, -12)	-13 (-72, 45.7)	-46 (-150, 58.6)
4	-27 (-54, 1)	-25 (-59, 9.2)	-7 (-67, 52.3)	19 (-87, 124.7)
5	-19 (-46, 9.1)	-18 (-53, 15.6)	16.9 (-41, 75.2)	47.1 (-58, 152.2)
6	-15 (-42, 12.1)	-15 (-49, 19.7)	41 (-19, 100.6)	-36 (-139, 67.6)
7	-16 (-41, 8.5)	3.9 (-30, 37.6)	10.5 (-47, 68.3)	1.3 (-101, 104)
8	5.4 (-21, 31.9)	-6 (-39, 26.1)	70.8 (12.6, 129.1)	44.4 (-58, 146.6)

Table C.8 Results for SO_4, multi-pollutant models, exposures anchored at conception and lagged from birth (as shown in Figure 5.4, purple circles). Risk differences for preterm birth with 0.25µg/m3 increases in sulfates (SO4) per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005. Adjusted for maternal race, education level, marital status, age at delivery, co-occurring ozone, elemental carbon, organic carbons, and nitrates.

Week of pregnancy in which exposure occurred	ExPTB	VPTB	MPTB	LPTB
1	7 (-26, 39.5)	55.8 (14.5, 97.1)	50.7 (-19, 120.6)	176.4 (54.1, 298.6)
2	31.8 (0, 64)	48.4 (7, 89.8)	57.4 (-13, 127.5)	159.1 (36.8, 281.4)
3	21.8 (-11, 54.2)	38 (-3, 79.2)	95.3 (24, 166.6)	71.2 (-51, 193.3)
4	13.7 (-17, 44.6)	73 (30.8, 115.1)	139.5 (67.9, 211.1)	250.8 (126.6, 375)
5	32.2 (0, 64.4)	72.9 (31.3, 114.4)	130 (59, 201)	173.6 (51.3, 295.8)
6	21 (-10, 52.4)	85.6 (43.9, 127.2)	125.9 (55.4, 196.4)	190 (67.9, 312.1)
7	3.4 (-28, 35.3)	90.7 (48.5, 133)	154.2 (83.1, 225.3)	289.9 (167.5, 412.4)
8	8.6 (-23, 40.4)	79.9 (37.7, 122.1)	107.5 (37.6, 177.5)	339.8 (217.5, 462.1)
9	4 (-28, 36)	84.9 (43.5, 126.2)	162.3 (92.1, 232.5)	319.8 (196.8, 442.9)
10	-13 (-43, 17.6)	67 (25.8, 108.2)	123.8 (54.1, 193.5)	390.7 (267.8, 513.6)
11	13.2 (-18, 44.4)	76.4 (35.8, 117)	176.8 (106.8, 246.9)	302 (180.4, 423.6)
12	17.3 (-14, 48.6)	32.8 (-7, 72.6)	163.3 (93.3, 233.3)	245.7 (124.8, 366.6)
13	21.7 (-11, 53.9)	34.5 (-5, 73.8)	48.1 (-20, 116.1)	260.8 (140.7, 381)
14	45.7 (13.2, 78.1)	31.2 (-9, 71.8)	101.1 (32.6, 169.6)	288.4 (167.2, 409.6)
15	32.6 (0.7, 64.4)	51.6 (11.4, 91.7)	137.4 (68.3, 206.6)	393.7 (272.3, 515.1)
16	30.8 (-1, 62.5)	68.3 (27.2, 109.4)	93.6 (24.9, 162.4)	299.4 (178.7, 420.1)
17	45.8 (13.6, 77.9)	50.1 (10.1, 90.2)	57.1 (-11, 124.8)	286.6 (165.9, 407.2)
18	46.3 (13.7, 78.8)	56.6 (16.4, 96.9)	118.6 (49.7, 187.6)	295.2 (174.5, 415.8)
19	56.2 (23.8, 88.7)	36 (-4, 75.9)	160.2 (90.7, 229.8)	261 (139.9, 382)
20	64.5 (32.2, 96.8)	50.8 (10.2, 91.4)	114.3 (44.5, 184.2)	233.4 (112.3, 354.6)
21		51.9 (10.7, 93.1)	135.1 (65.3, 204.8)	361.3 (239.2, 483.4)
22		77.1 (36.4, 117.7)	123.1 (53.5, 192.6)	472 (349.6, 594.5)
23		65.1 (24.5, 105.7)	92 (23.2, 160.8)	403.2 (282.2, 524.1)
24		70.4 (30.4, 110.4)	130.9 (63.1, 198.7)	405.2 (285.8,

				524.6)
25		39.1 (0.2, 77.9)	167.1 (98.8, 235.4)	406.8 (288.6, 524.9)
26		14.8 (-24, 53.3)	143.5 (75.8, 211.1)	353.8 (235.9, 471.7)
27		3.6 (-35, 42)	158.2 (89.8, 226.7)	372.2 (253.8, 490.6)
28		28.8 (-11, 68.1)	145.5 (78, 213)	411 (291.8, 530.2)
29			150.5 (84.3, 216.7)	364 (246.2, 481.8)
30			121.2 (54.8, 187.5)	342.5 (225.7, 459.3)
31			140.5 (73.9, 207)	404 (287.6, 520.5)
32			139 (72.6, 205.4)	358.7 (243.4, 474)
33				335.8 (220.4, 451.3)
34				304.2 (189.1, 419.2)
35				408.1 (288.1, 528.1)

Exposure lagged from birth by week	ExPTB	VPTB	MPTB	LPTB
0	-10 (-39, 18.8)	-26 (-64, 13.3)	45.6 (-21, 111.7)	250.7 (135.6, 365.8)
1	-15 (-44, 14.3)	-27 (-66, 11.4)	30.5 (-35, 96.2)	209.6 (97, 322.3)
2	-19 (-47, 9.7)	-57 (-94, -19)	21.2 (-44, 86.7)	119.6 (5, 234.2)
3	-20 (-48, 8.9)	-60 (-96, -23)	-15 (-80, 49.9)	17.2 (-99, 133.2)
4	-23 (-54, 7)	-37 (-74, 1)	-7 (-73, 59.7)	51.6 (-66, 169.4)
5		-19 (-56, 18.7)	2.5 (-63, 67.6)	142.2 (25.2, 259.1)
6		-19 (-57, 19.4)	32.3 (-34, 98.7)	58.2 (-57, 173.4)
7		7.5 (-30, 45.2)	10.5 (-54, 75.4)	95.1 (-20, 209.8)
8		-7 (-43, 29.2)	78.9 (13.6, 144.2)	167 (53, 281)

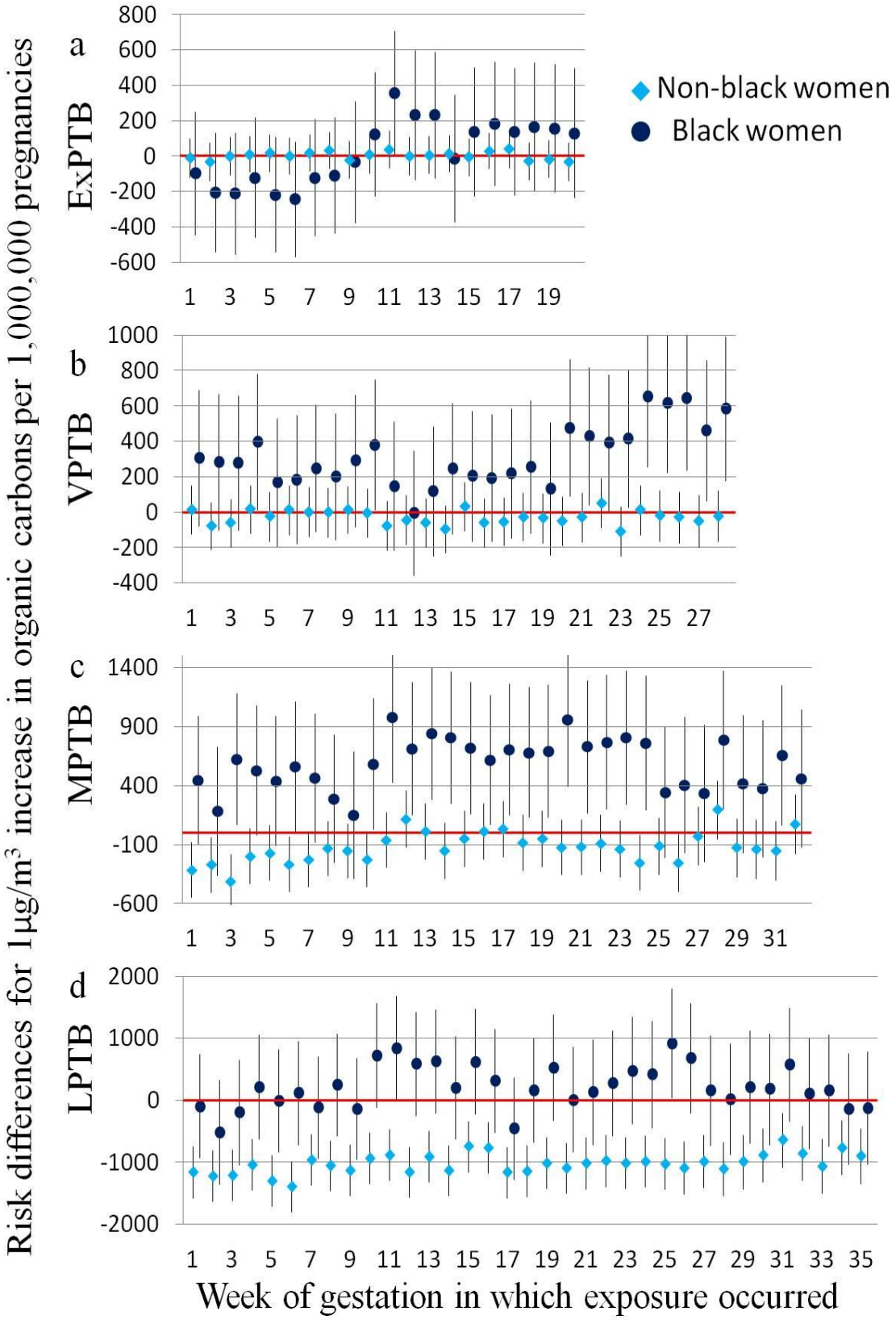

Risk differences for 1μg/m³ increase in organic carbons per 1,000,000 pregnancies
a
ExPTB
800
600
400
200
0
-200
-400
-600
1 3 5 7 9 11 13 15 17 19
Non-black women
Black women
b
VPTB
1000
800
600
400
200
0
-200
-400
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
1400
900
400
-100
-600
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
2000
1000
0
-1000
-2000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred

Figure C.1: Effect measure modification by black race for organic carbons. Risk differences for 1μg/m^3 increases in OC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at time of conception. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

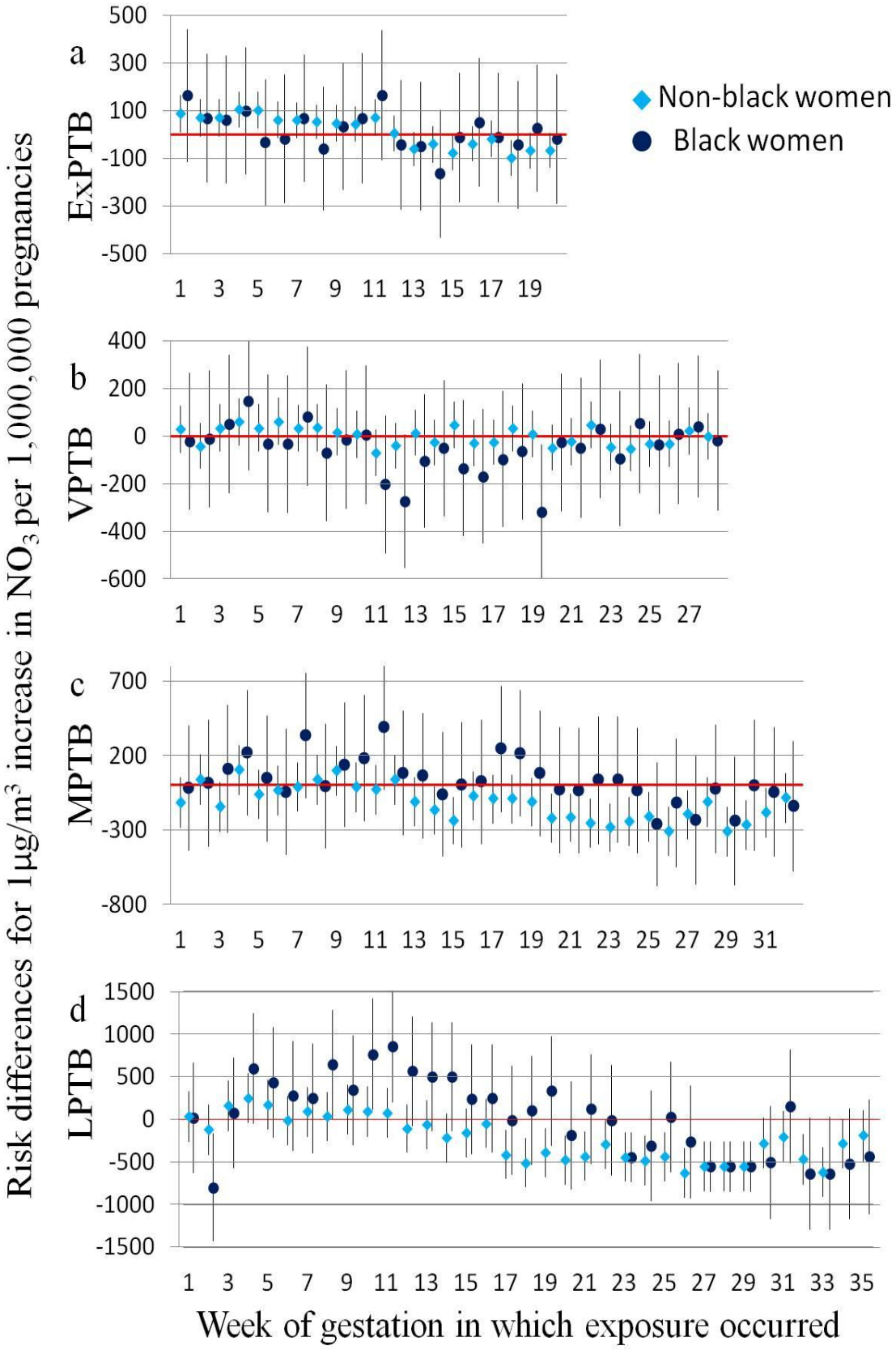

Risk differences for 1μg/m³ increase in NO3 per 1,000,000 pregnancies
a
ExPTB
500
300
100
-100
-300
-500
1 3 5 7 9 11 13 15 17 19
b
VPTB
400
200
0
-200
-400
-600
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
700
200
-300
-800
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
1500
1000
500
0
-500
-1000
-1500
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred
Non-black women
Black women

Figure C.2: Effect measure modification by black race for NO_3. Risk differences for $1\mu g/m^3$ increases in NO_3 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at time of conception. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

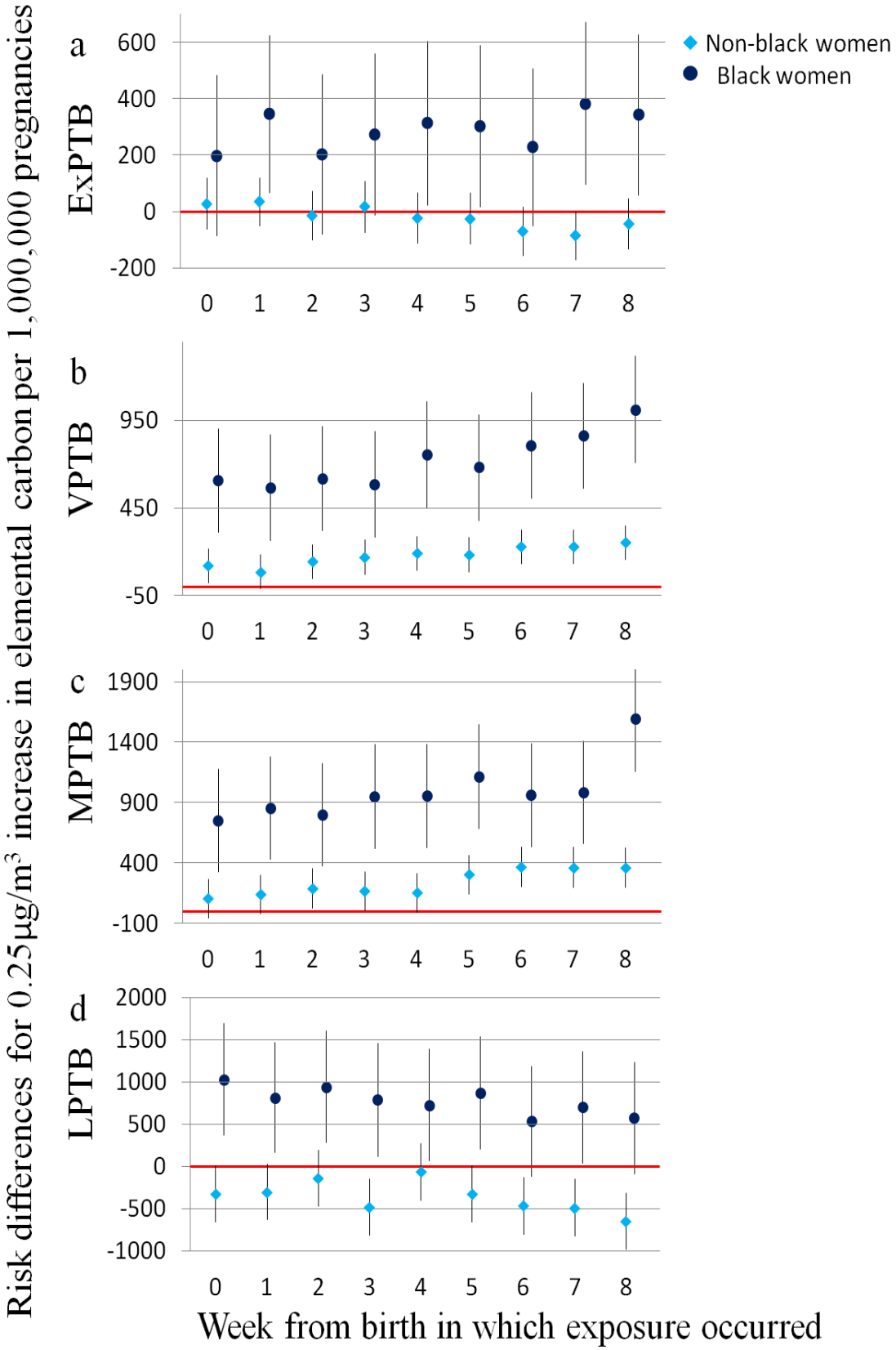

Risk differences for 0.25µg/m³ increase in elemental carbon per 1,000,000 pregnancies
a
ExPTB
600
400
200
0
-200
b
VPTB
950
450
-50
c
MPTB
1900
1400
900
400
-100
d
LPTB
2000
1500
1000
500
0
-500
-1000
0 1 2 3 4 5 6 7 8
Non-black women
Black women
Week from birth in which exposure occurred

Figure C.3: Effect measure modification by black race for elemental carbon, lagged exposures. Risk differences for 0.25 µg/m3 increases in EC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

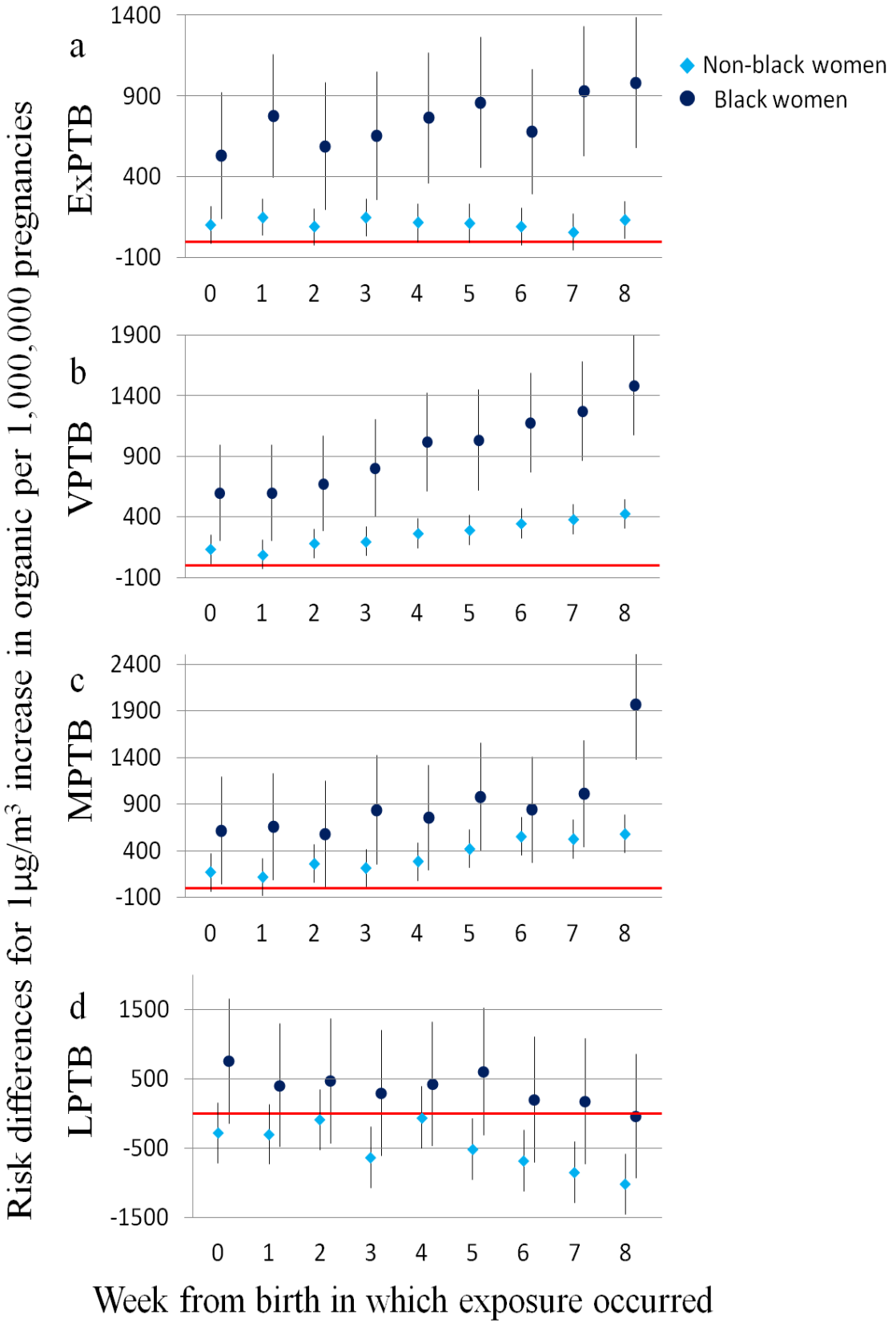

Risk differences for 1μg/m³ increase in organic per 1,000,000 pregnancies
a
ExPTB
1400
900
400
-100
0 1 2 3 4 5 6 7 8
b
VPTB
1900
1400
900
400
-100
0 1 2 3 4 5 6 7 8
c
MPTB
2400
1900
1400
900
400
-100
0 1 2 3 4 5 6 7 8
d
LPTB
1500
500
-500
-1500
0 1 2 3 4 5 6 7 8
Non-black women
Black women
Week from birth in which exposure occurred

Figure C.4: Effect measure modification by black race for organic carbons, lagged exposures. Risk differences for 1 $\mu g/m^3$ increases in OC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

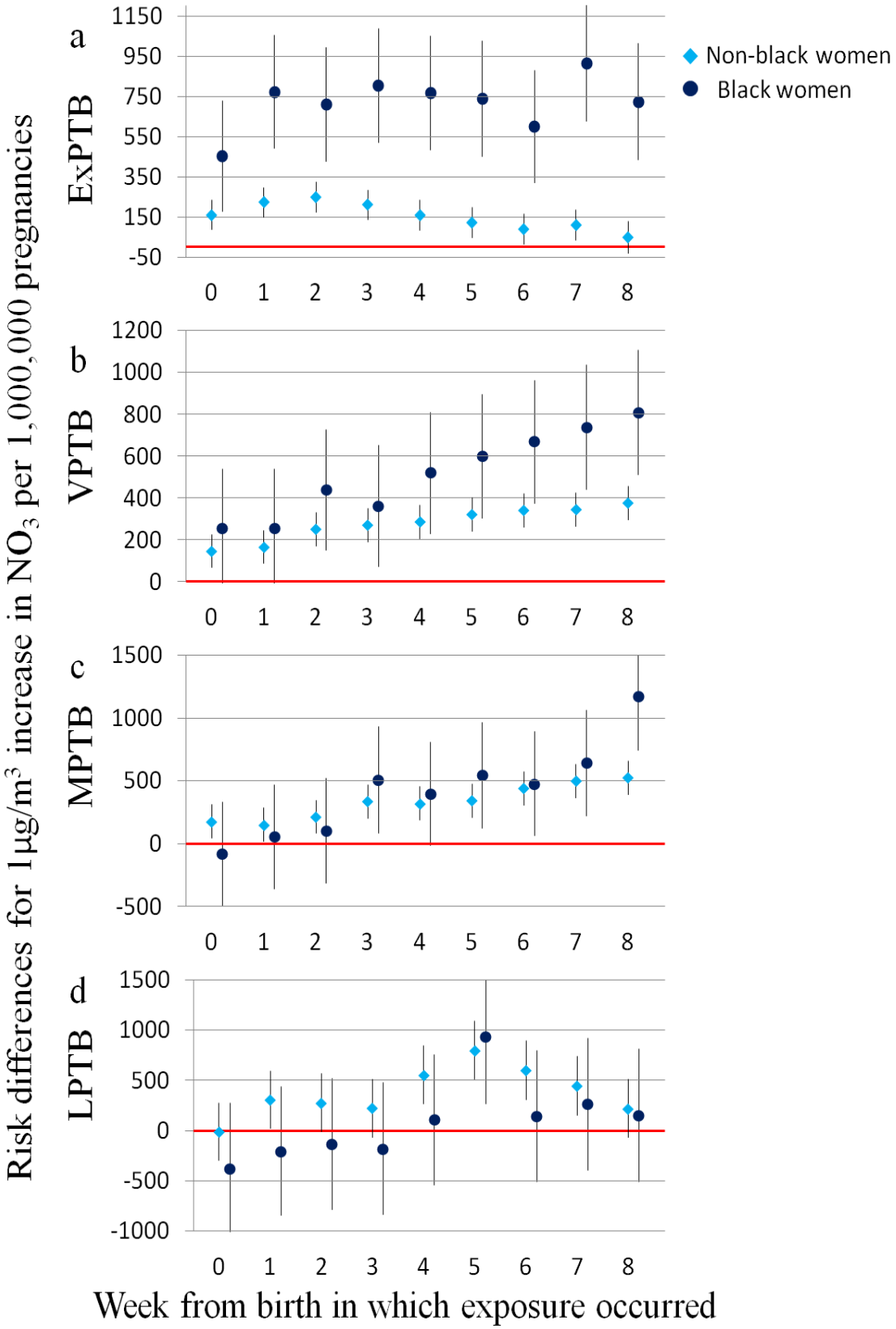

a
ExPTB
1150
950
750
550
350
150
-50
0 1 2 3 4 5 6 7 8
b
VPTB
1200
1000
800
600
400
200
0
0 1 2 3 4 5 6 7 8
c
MPTB
1500
1000
500
0
-500
0 1 2 3 4 5 6 7 8
d
LPTB
1500
1000
500
0
-500
-1000
0 1 2 3 4 5 6 7 8
Non-black women
Black women
Risk differences for 1μg/m³ increase in NO3 per 1,000,000 pregnancies
Week from birth in which exposure occurred

Figure C.5: Effect measure modification by black race for NO_3, lagged exposures. Risk differences for 1 $\mu g/m^3$ increases in NO_3 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

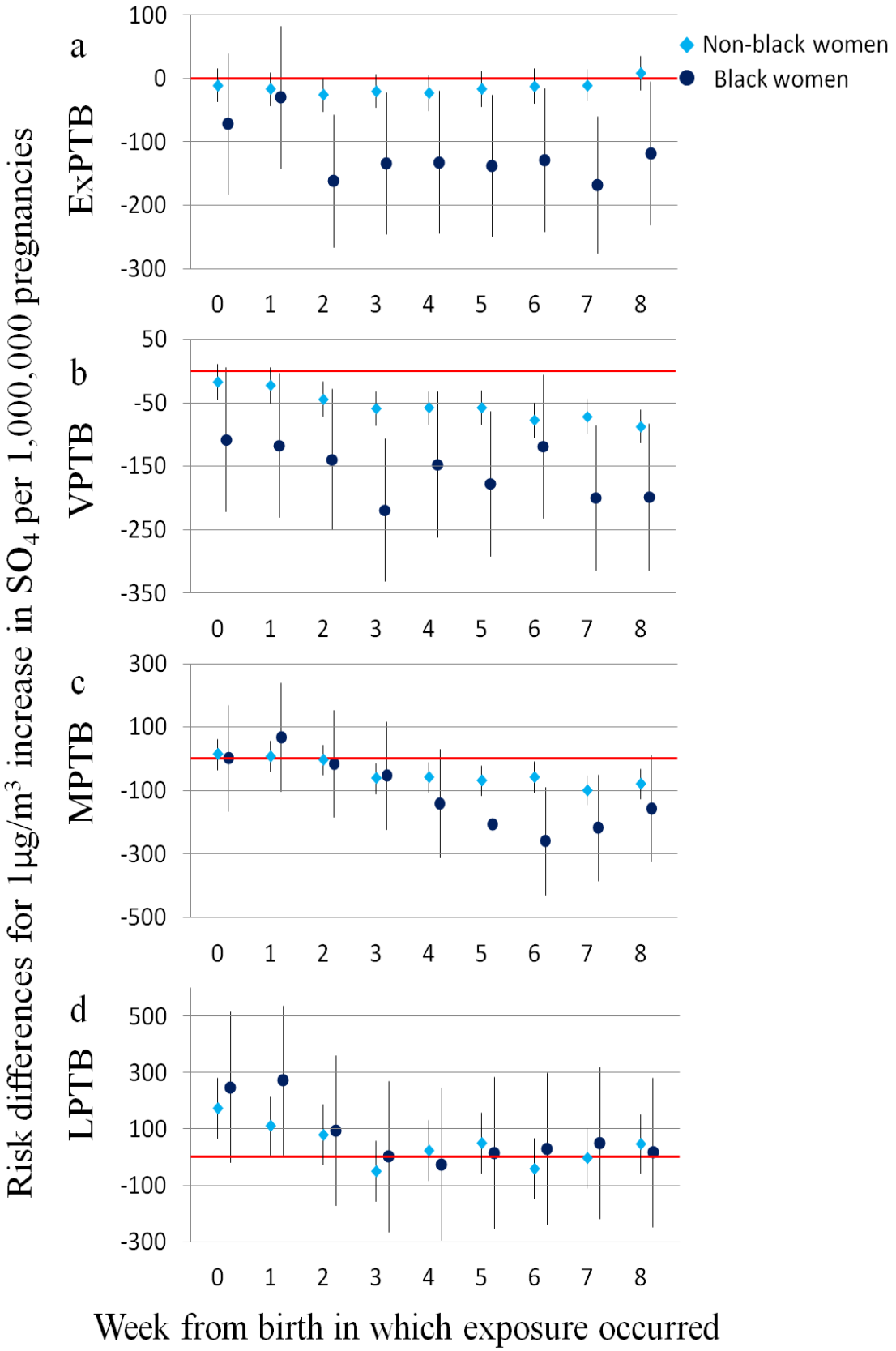

Risk differences for 1μg/m³ increase in SO4 per 1,000,000 pregnancies
a
ExPTB
b
VPTB
c
MPTB
d
LPTB
Non-black women
Black women
100
0
-100
-200
-300
50
-50
-150
-250
-350
300
100
-100
-300
-500
500
300
100
-100
-300
0 1 2 3 4 5 6 7 8
Week from birth in which exposure occurred

Figure C.6: Effect measure modification by black race for SO_4, lagged exposures. Risk differences for 1 $\mu g/m^3$ increases in SO_4 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for black women (dark blue circle) and non-black women (light blue diamond). Models adjusted for education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

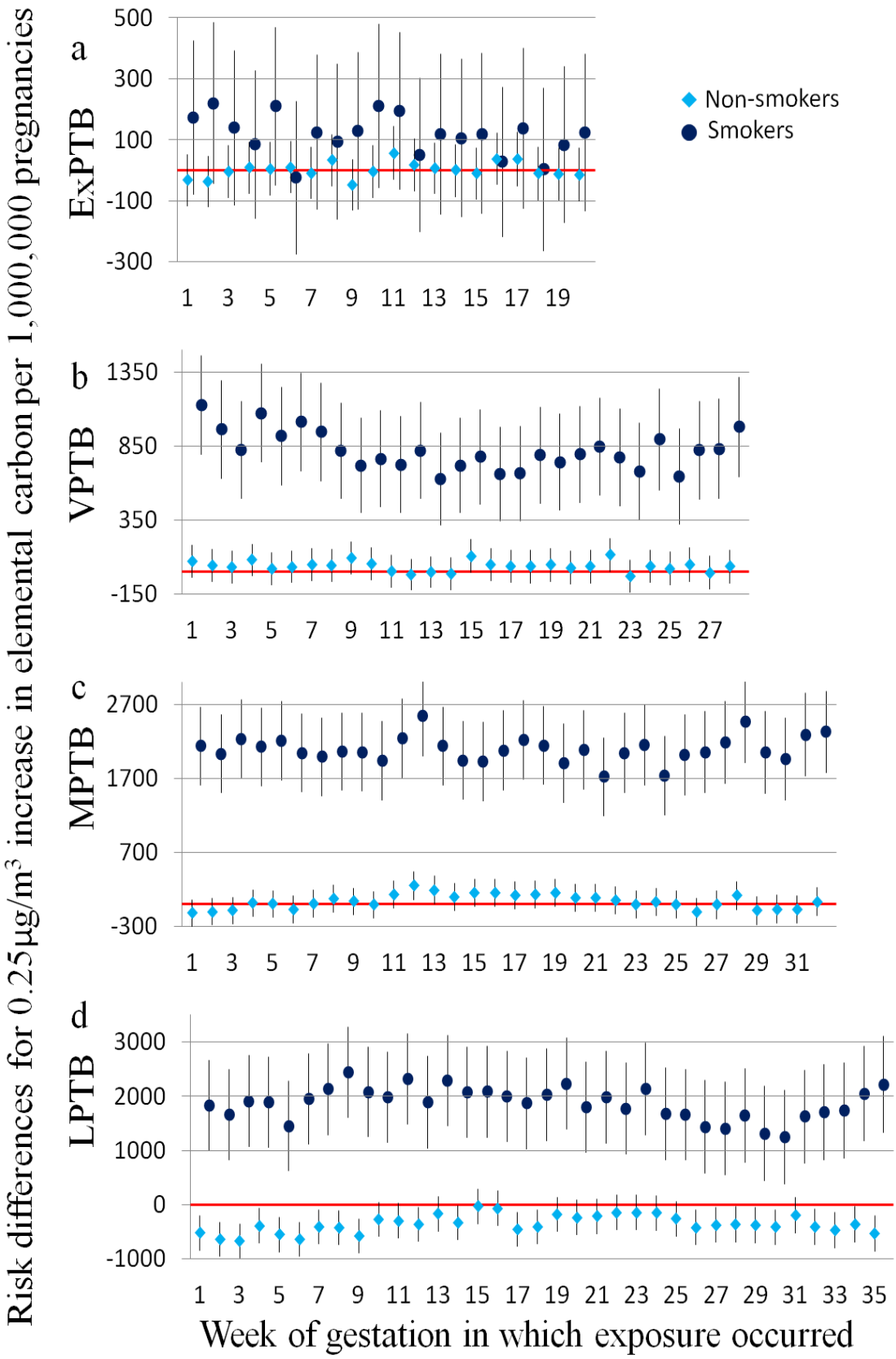

Risk differences for 0.25 μg/m³ increase in elemental carbon per 1,000,000 pregnancies
a
ExPTB
500
300
100
-100
-300
1 3 5 7 9 11 13 15 17 19
Non-smokers
Smokers
b
VPTB
1350
850
350
-150
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
2700
1700
700
-300
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
3000
2000
1000
0
-1000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred

Figure C.7: Effect measure modification by smoking status for elemental carbon, exposures anchored at conception. Risk differences for 0.25 $\mu g/m^3$ increases in EC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at date of conception. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

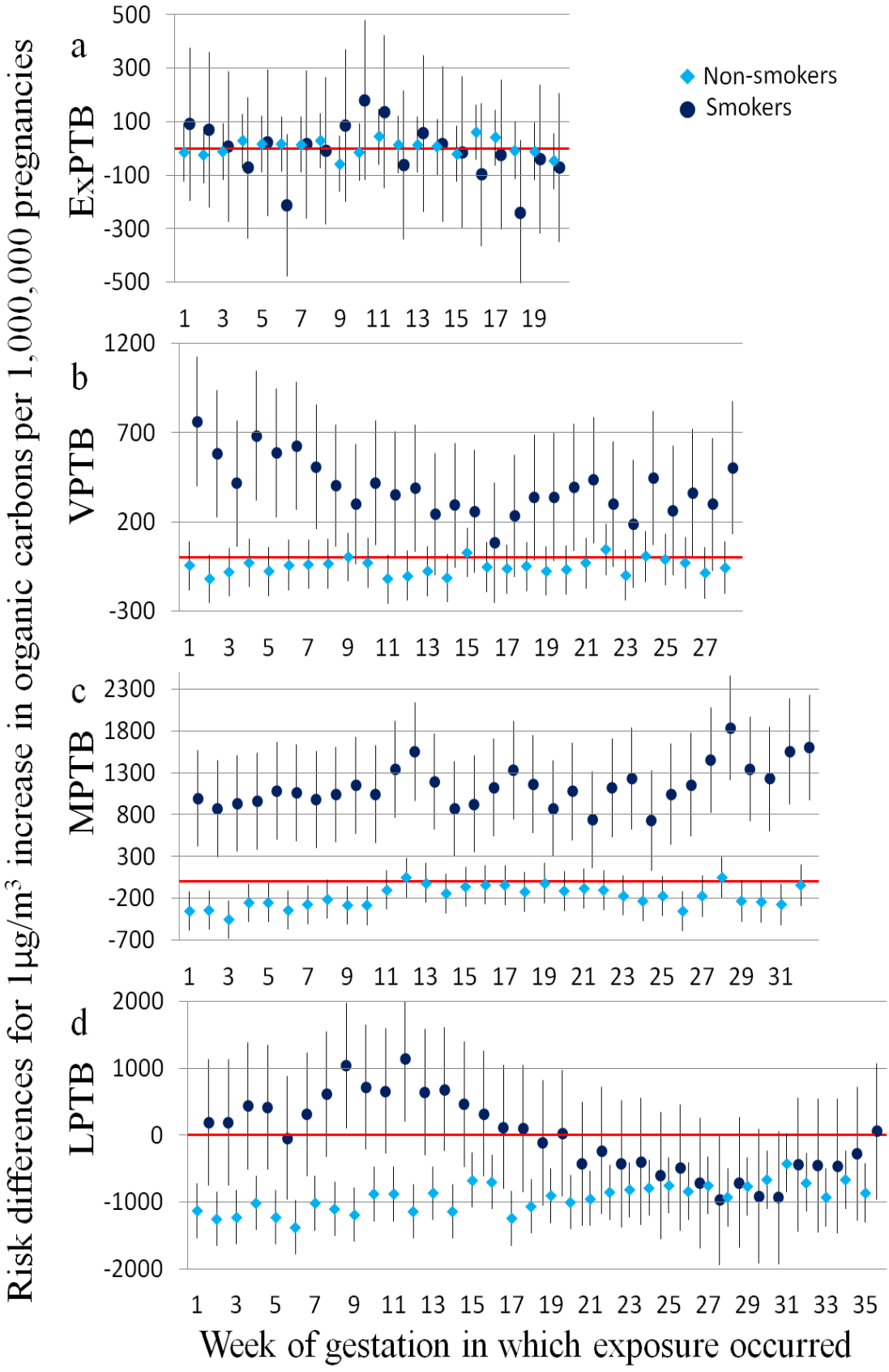

Risk differences for 1μg/m³ increase in organic carbons per 1,000,000 pregnancies
a
ExPTB
500
300
100
-100
-300
-500
1 3 5 7 9 11 13 15 17 19
Non-smokers
Smokers
b
VPTB
1200
700
200
-300
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
2300
1800
1300
800
300
-200
-700
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
2000
1000
0
-1000
-2000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred

Figure C.8: Effect measure modification by smoking status for organic carbons, exposures anchored at conception. Risk differences for 1 μg/m^3 increases in OC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at date of conception. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

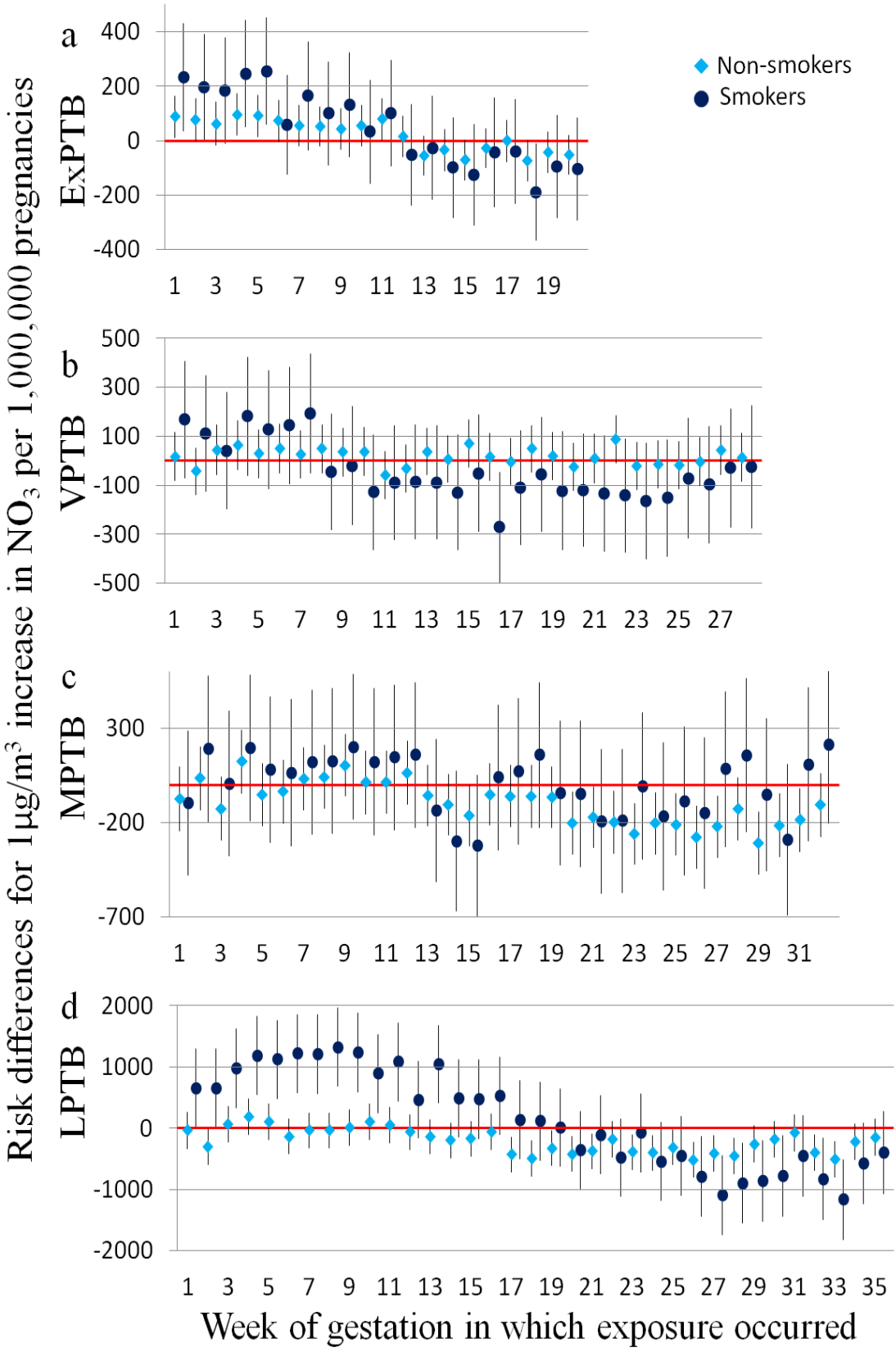

a
ExPTB
400
200
0
-200
-400
1 3 5 7 9 11 13 15 17 19
Non-smokers
Smokers
b
VPTB
500
300
100
-100
-300
-500
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
300
-200
-700
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
2000
1000
0
-1000
-2000
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Week of gestation in which exposure occurred
Risk differences for 1μg/m3 increase in NO3 per 1,000,000 pregnancies

Figure C.9: Effect measure modification by smoking status for NO_3, exposures anchored at conception. Risk differences for 1 $\mu g/m^3$ increases in NO_3 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at date of conception. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

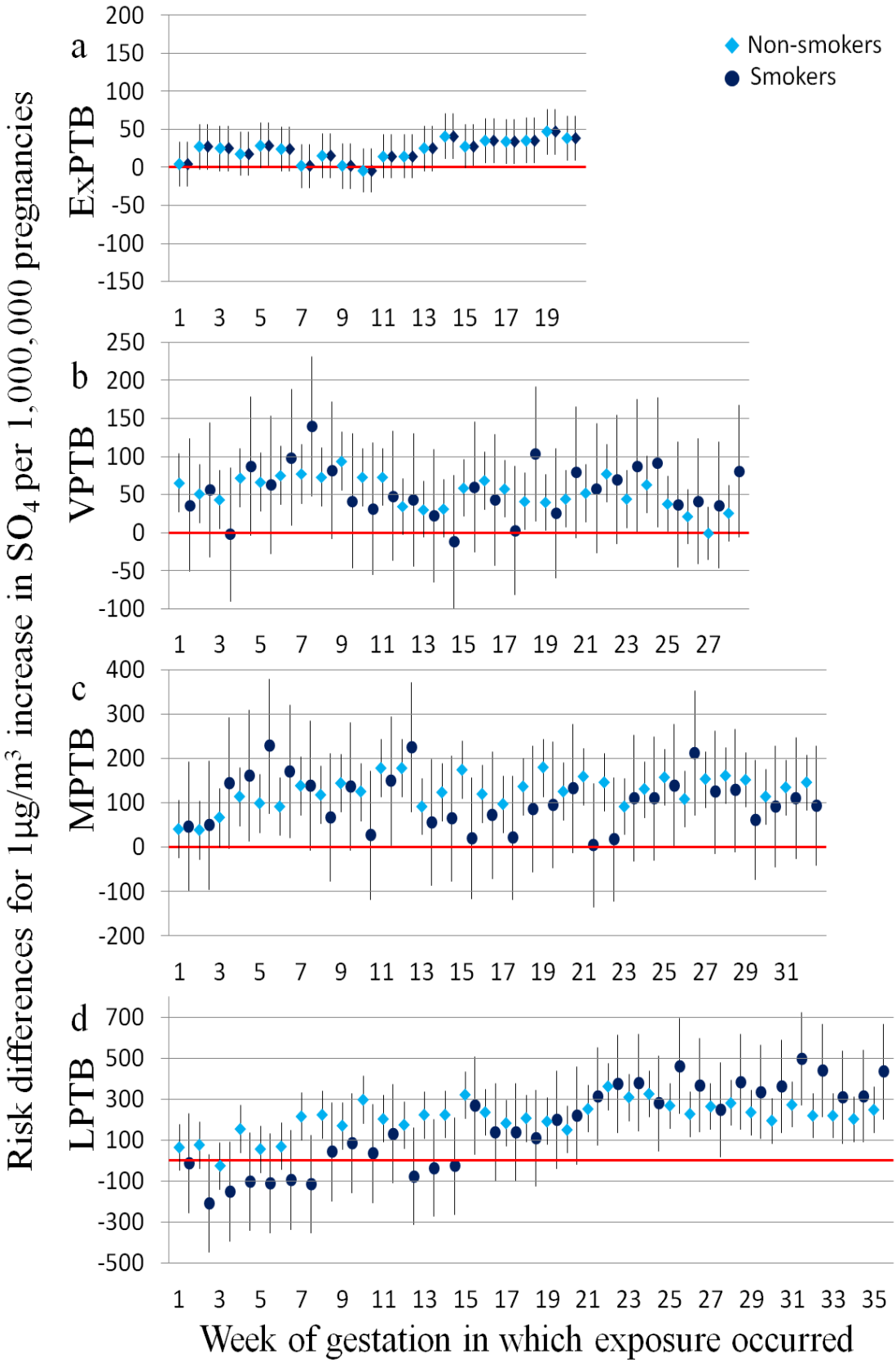

Non-smokers
Smokers
a
ExPTB
200
150
100
50
0
-50
-100
-150
1 3 5 7 9 11 13 15 17 19
b
VPTB
250
200
150
100
50
0
-50
-100
1 3 5 7 9 11 13 15 17 19 21 23 25 27
c
MPTB
400
300
200
100
0
-100
-200
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
d
LPTB
700
500
300
100
-100
-300
-500
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Risk differences for 1 μg/m3 increase in SO4 per 1,000,000 pregnancies
Week of gestation in which exposure occurred

Figure C.10: Effect measure modification by smoking status for SO_4, exposures anchored at conception. Risk differences for 1 $\mu g/m^3$ increases in SO_4 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are anchored at date of conception. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

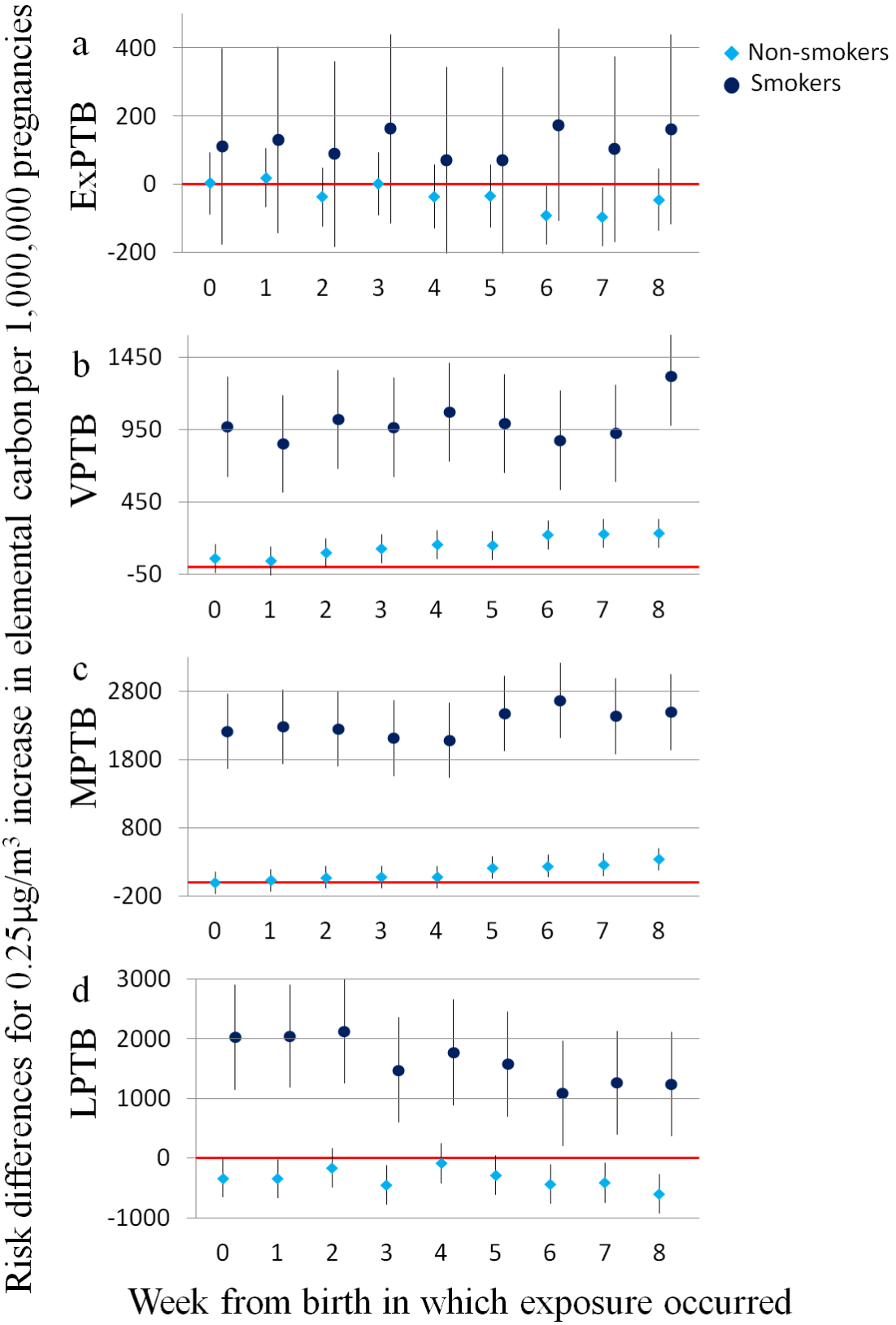

Risk differences for 0.25µg/m³ increase in elemental carbon per 1,000,000 pregnancies
a
ExPTB
400
200
0
-200
0 1 2 3 4 5 6 7 8
b
VPTB
1450
950
450
-50
0 1 2 3 4 5 6 7 8
c
MPTB
2800
1800
800
-200
0 1 2 3 4 5 6 7 8
d
LPTB
3000
2000
1000
0
-1000
0 1 2 3 4 5 6 7 8
Non-smokers
Smokers
Week from birth in which exposure occurred

Figure C.11: Effect measure modification by smoking status for elemental carbon, lagged exposures. Risk differences for 0.25 μg/m^3 increases in EC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

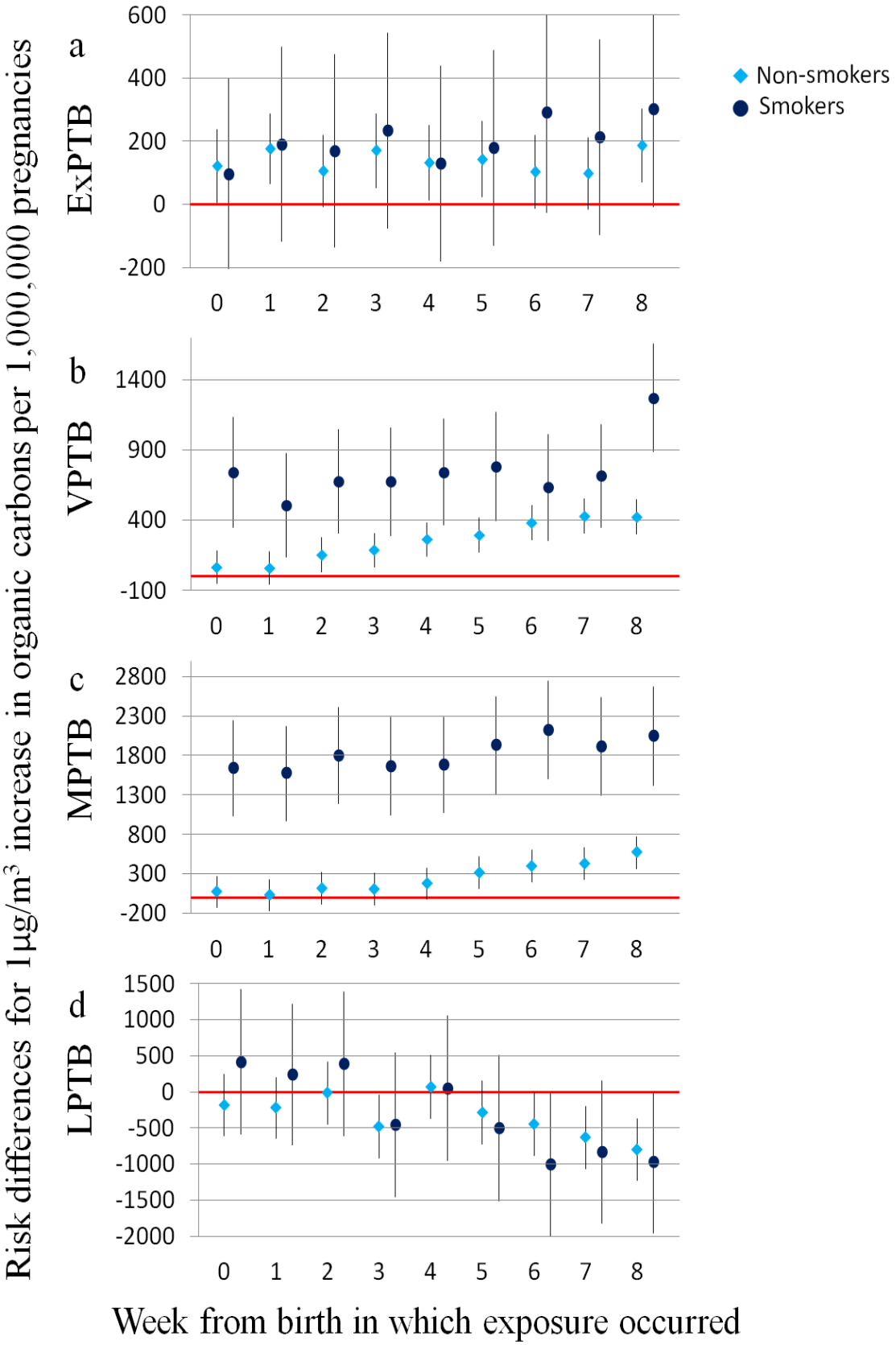

Risk differences for 1μg/m³ increase in organic carbons per 1,000,000 pregnancies
a
ExPTB
600
400
200
0
-200
0 1 2 3 4 5 6 7 8
b
VPTB
1400
900
400
-100
0 1 2 3 4 5 6 7 8
c
MPTB
2800
2300
1800
1300
800
300
-200
0 1 2 3 4 5 6 7 8
d
LPTB
1500
1000
500
0
-500
-1000
-1500
-2000
0 1 2 3 4 5 6 7 8
Non-smokers
Smokers
Week from birth in which exposure occurred

Figure C.12: Effect measure modification by smoking status for organic carbons, lagged exposures. Risk differences for 1 $\mu g/m^3$ increases in OC per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

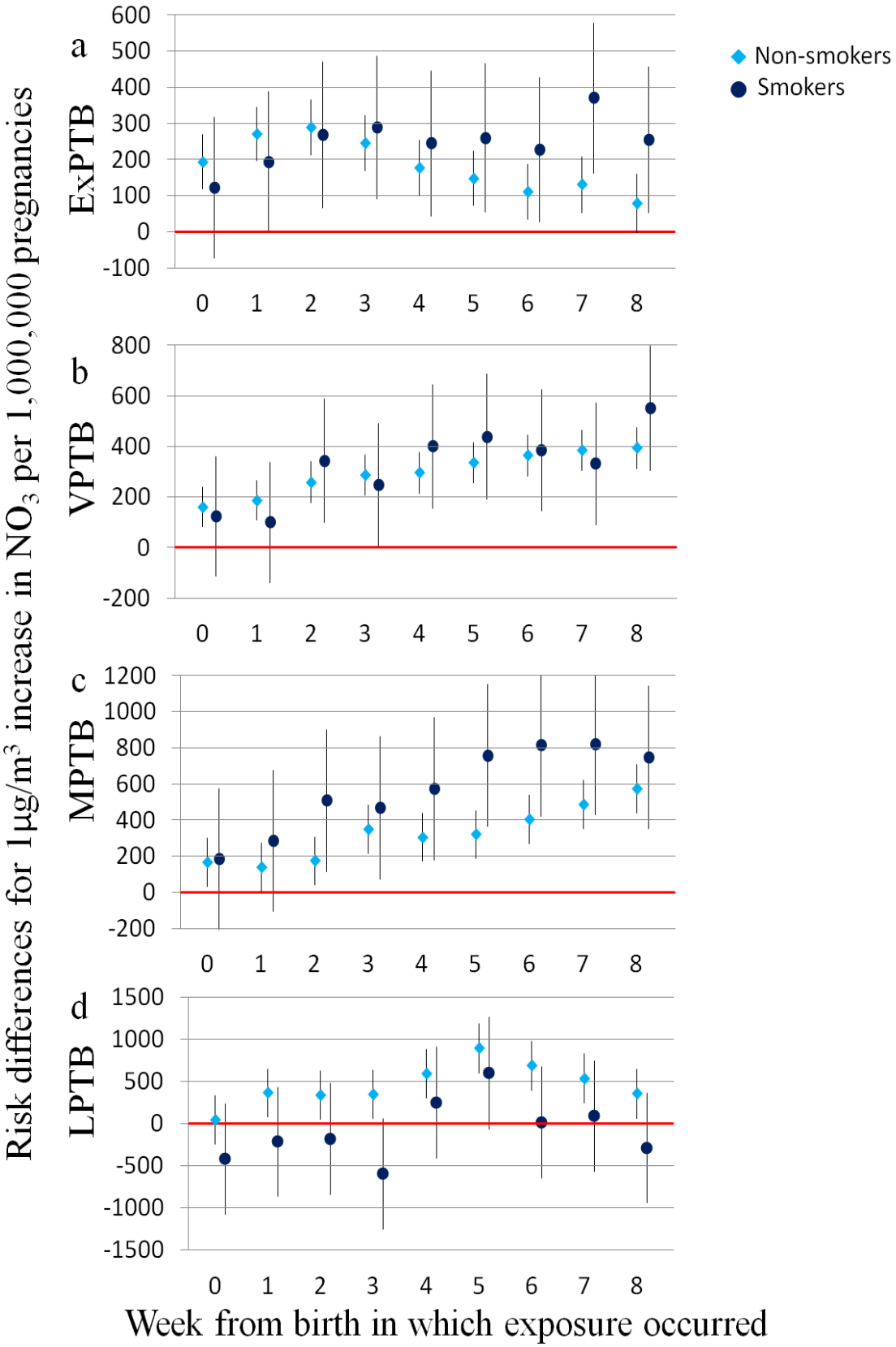

Risk differences for 1μg/m³ increase in NO3 per 1,000,000 pregnancies
a
ExPTB
b
VPTB
c
MPTB
d
LPTB
Non-smokers
Smokers
Week from birth in which exposure occurred

Figure C.13: Effect measure modification by smoking status for NO_3, lagged exposures. Risk differences for 1 µg/m3 increases in NO_3 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

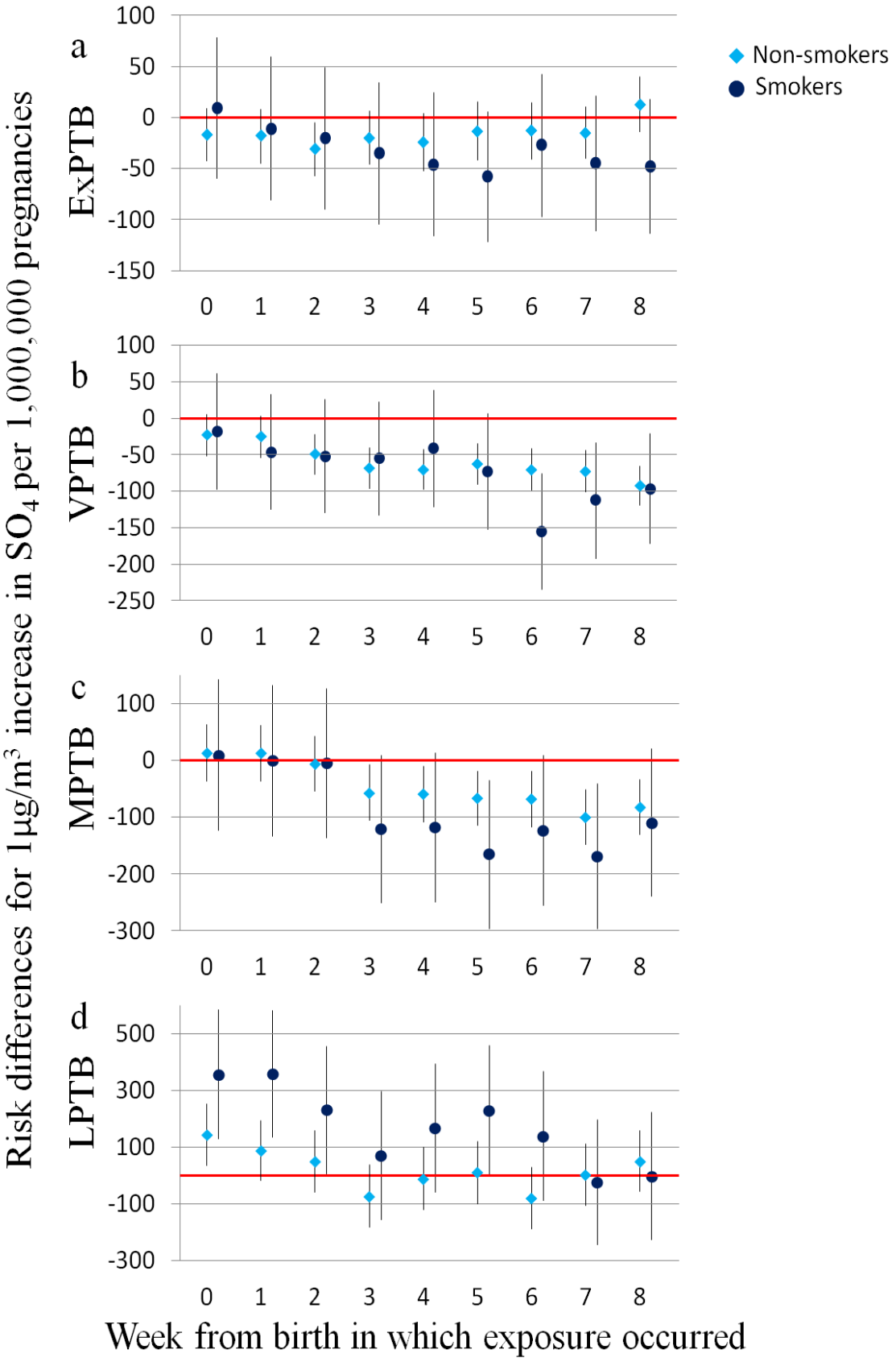

Risk differences for 1μg/m³ increase in SO4 per 1,000,000 pregnancies
a
ExPTB
b
VPTB
c
MPTB
d
LPTB
Non-smokers
Smokers
Week from birth in which exposure occurred

Figure C.14: Effect measure modification by smoking status for SO_4, lagged exposures. Risk differences for 1 $\mu g/m^3$ increases in SO_4 per 1,000,000 pregnancies for women residing in OH, PA, or NJ with pregnancies at risk of preterm birth from Jan 1, 2000 to Dec 31, 2005 for smokers (dark blue circle) and non-smokers (light blue diamond). Models adjusted for maternal race, education level, marital status, age at delivery, and co-occurring ozone. Exposures are lagged from date of birth. Outcomes are as follows: a) outcome = risk of birth at 20-27 weeks of gestation (ExPTB), (b) outcome = risk of birth at 28-31 weeks of gestation (VPTB), (c) outcome = risk of birth at 32-34 weeks of gestation (MPTB), and (d) outcome = risk of birth at 35-36 weeks of gestation (LPTB).

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