



# HHS PUBLIC ACCESS

Author manuscript

*J Allergy Clin Immunol.* Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

*J Allergy Clin Immunol.* 2016 August ; 138(2): 432–440.e5. doi:10.1016/j.jaci.2015.12.1309.

## Preterm birth and air pollution: Critical windows of exposure for women with asthma

Pauline Mendola, Ph.D.<sup>1</sup>, Maeve Wallace, Ph.D.<sup>1</sup>, Beom Seuk Hwang, Ph.D.<sup>1</sup>, Danping Liu, Ph.D.<sup>1</sup>, Candace Robledo, Ph.D.<sup>2</sup>, Tuija Männistö, M.D., Ph.D.<sup>3</sup>, Rajeshwari Sundaram, Ph.D.<sup>1</sup>, Seth Sherman, Ph.D.<sup>4</sup>, Qi Ying, Ph.D.<sup>5</sup>, and Katherine L. Grantz, M.D., M.S.<sup>1</sup>

<sup>1</sup>Eunice Kennedy Shriver National Institute of Child Health and Human Development, Division of Intramural Population Health Research, Rockville, MD 20852 USA <sup>2</sup>University of North Texas Health Science Center, Department of Behavioral and Community Health, Fort Worth, TX 76107 USA <sup>3</sup>Department of Chronic Disease Prevention, National Institute for Health and Welfare, Oulu, Finland; Northern Finland Laboratory Centre Nordlab, Oulu, Finland; and Department of Clinical Chemistry, University of Oulu, Oulu, Finland <sup>4</sup>The Emmes Corporation, Rockville, MD 20852 USA <sup>5</sup>Texas A&M University, Zachary Department of Civil Engineering, College Station, TX 77845 USA

### Abstract

**Background**—Ambient air pollutants may increase preterm birth (PTB) risk but critical exposure windows are uncertain. The interaction of asthma and pollutant exposure is rarely studied.

**Objective**—To assess the interaction of maternal asthma and air pollutant exposures in relation to PTB risk.

**Methods**—Electronic medical records for 223,502 U.S. deliveries were linked with modified Community Multiscale Air Quality model outputs. Logistic regression with generalized estimating equations estimated the odds ratio (OR) and 95% confidence intervals (CI) for PTB based on the interaction of maternal asthma and particulate matter <2.5 microns (PM<sub>2.5</sub>) and <10 microns (PM<sub>10</sub>), ozone (O<sub>3</sub>), nitrogen oxides (NO<sub>x</sub>), sulfur dioxide (SO<sub>2</sub>) and carbon monoxide (CO) per interquartile range. For each gestational week 23–36, exposures among women who delivered were compared to those remaining pregnant. Three-months preconception, whole pregnancy, weeks 1–28 and the last six weeks of gestation averages were also evaluated.

**Results**—Assessing PTB by gestational week, significant asthma interactions were sporadic before 30 weeks but more common during weeks 34–36 with higher risk among asthmatic mothers

---

Address correspondence to: Pauline Mendola, Ph.D., *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Division of Intramural Population Health Research, 6100 Executive Blvd, Room 7B03F, Rockville, MD 20852. Phone: 301-496-5267; Mobile: 301-905-6118; Fax: 301-402-2084; pauline.mendola@nih.gov.

**Declaration of interests:** The authors declare no financial or personal interests that would influence the findings or interpretation of these data. Word count (Text): 3561/3500

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

for NO<sub>x</sub>, CO and SO<sub>2</sub> exposure and an inverse association with O<sub>3</sub> in week 34. Odds of PTB were significantly higher among asthmatics for CO and NO<sub>x</sub> preconception and early in pregnancy. In the last six weeks of pregnancy, PM<sub>10</sub> risk for PTB was higher among asthmatics.

**Conclusion**—Asthmatic mothers may experience higher risk for PTB after exposure to traffic-related pollutants such as CO and NO<sub>x</sub> particularly for exposures three-months preconception and in the early weeks of pregnancy.

### Keywords

Asthma; pregnancy; preterm birth; air pollution

---

### Introduction

Environmental factors that contribute to adverse pregnancy outcomes have received considerable attention, and the current literature regarding risk of preterm birth at <37 weeks' gestation is well summarized in several recent review articles (1–5). Overall, the evidence for higher preterm birth risk associated with ambient air pollution is mixed, but third trimester exposure to carbon monoxide (CO) and particulate matter with aerodynamic diameter <10 microns (PM<sub>10</sub>) was significantly associated with higher preterm birth risk in a recent meta-analysis (2). Other summaries and pooled estimates suggested significantly higher risks associated with a range of exposure windows for particulate matter with aerodynamic diameter <2.5 microns (PM<sub>2.5</sub>) (3;4) and sulfur dioxide (SO<sub>2</sub>) (3). Air toxics, particularly polycyclic aromatic hydrocarbons (PAHs), may also be related to early delivery (1).

Despite the effort in this area (6), no etiologically-relevant critical exposure time-window for ambient air to influence preterm birth risk has been determined and the varied time windows make comparisons between studies more difficult. A wide range of air pollution exposure estimates have been used, ranging from whole pregnancy averages (7;8;9), trimester-specific results (8–12) to months (13) or weeks (14–16) before delivery. Several studies evaluated multiple windows (9;17–19) and in some early studies, the relevant windows were unclear (7). Heterogeneity in study design and exposure metrics may be part of the issue behind the lack of consistency in findings across studies (20;21).

Further adding to the complexity is the likelihood that pregnant women are not uniformly susceptible to the impact of air pollutants and women with asthma may be particularly vulnerable. Asthma exacerbation and perhaps incidence are related to poor air quality (22). Asthma prevalence is estimated to be more than 9% among American women (23) and maternal asthma is a well-known risk factor for preterm birth (24), a finding also observed in our data (25). A study of birth records from 1988–2006, conducted in Stockholm, Sweden, found significant preterm birth risks for mothers with and without asthma associated with first trimester ozone (O<sub>3</sub>) exposure, but observed no main effect or interaction with asthma for first trimester nitrogen oxides (NO<sub>x</sub>) exposure (26). Other susceptible subpopulations like the elderly or diabetic persons appear to respond differentially to exposure, (27) but air pollution effects have also been muted among individuals with preexisting disease.(28) Given that the world-wide impact of asthma on the lives of young women continues to

increase (29) and challenges to control air pollution remain, whether or not pregnant asthmatics are also a susceptible subpopulation is an important avenue for investigation.

To address these data gaps, we evaluated the impact of exposure to criteria air pollutants on the week-by-week risk of preterm birth and for a range of exposure windows in a large, contemporary US obstetric cohort of women with and without asthma.

## Methods

### Study population

Gestational age, maternal demographics, medical, reproductive and prenatal history, and a summary of labor and delivery information were ascertained in the Consortium on Safe Labor (CSL, 2002–2008) (30). This retrospective cohort of births at 23 weeks' gestation was assembled using electronic medical records from 12 centers (19 hospitals) across the US (Figure 1). The cohort included 228,562 deliveries with 233,736 newborns, with 87% of births occurring during 2005–2007. We excluded multifetal pregnancies (n=5,050) and pregnancies missing air quality data (n=10), resulting in an analytic sample of 223,502 singleton pregnancies among 204,175 women. Most women (185,785; 91.0%) contributed only one pregnancy. The CSL was approved by the institutional review boards of all participating institutions. Data collection and validation have been previously described (30).

### Outcome and covariates

All outcome and covariate data were derived from the electronic delivery records and supplemented with International Classification of Diseases, version 9 (ICD-9) codes in the hospital discharge summaries. Preterm birth was defined using the best clinical gestational age recorded in the medical record. Births at each week from 23 to 36 of gestation were compared to ongoing pregnancies. We also examined preterm birth as a dichotomous variable with two cut-points, preterm birth (<37 weeks gestation) and early preterm birth (<34 weeks gestation). Asthma diagnosis was recorded in the medical record and/or in the discharge summary (ICD-9 code 493.-493.9). Adjusted models include maternal age in years (<20, 20–24, 25–29, 30–34, 35, unknown); race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other Race, Unknown), pre-pregnancy body mass index (BMI, kg/m<sup>2</sup>) (<18.5 underweight, 18.5–24.9 normal weight, 25–29.9 overweight, 30 obese, unknown), smoking and alcohol use (both yes/no), study site, parity (nulliparous, primiparous, multiparous), insurance status (private, public/government, self-pay/other, unknown), marital status (married, divorced/widowed, single, unknown), and maternal comorbidities (chronic hypertension, diabetes, thyroid disease and HIV). Covariates were selected *a priori* based on earlier analyses of preterm birth in association with maternal asthma (25;31).

### Exposure

Ambient air pollutant concentrations were estimated using a modified version of the Community Multiscale Air Quality (CMAQ) model (32), a three-dimensional, regional air quality model developed by the US Environmental Protection Agency (U.S. EPA). Meteorology inputs for the model simulations were generated using the Weather Research and Forecasting model, including inputs for hourly temperature, relative humidity and wind

characteristics. Air pollutant emissions were generated using the U.S. EPA National Emission Inventories. Hourly concentrations of ambient air pollutants for the ground-level layer (approximately 30 meters high) over the entire continental U.S. for years 2001–2009 were calculated in the Air Quality and Reproductive Health study. Because the CSL data are anonymized, these hourly concentrations were averaged to estimate the mean daily levels within each of the 15 distinct delivery hospital referral regions (33) which were then averaged to obtain weekly and whole pregnancy exposure estimates. The size of hospital referral regions ranged from 415 to 312,644 square kilometers. Estimates were weighted for population density to discount exposure in areas where women were unlikely to live or work. Modelled data were fused with observed monitor data retrieved from the U.S. EPA Air Quality System where available and estimates were adjusted using inverse distance weighting for criteria air pollutants: PM<sub>2.5</sub> and PM<sub>10</sub>, O<sub>3</sub>, NO<sub>x</sub>, SO<sub>2</sub> and CO. Our final model results were compared to pollutant level estimates obtained with four other commonly used strategies, including one based on monitors alone. Our fused, population-weighted model performed very well with better coverage for particles, SO<sub>2</sub> and O<sub>3</sub> than monitors alone and with stronger agreement with measured exposure for both gas phase and particle phase species than raw CMAQ models (34). Risk models are based on interquartile range (IQR; the difference between the 25–75 percentiles) changes in exposure (Supplemental Table 1).

### Statistical analyses

Each observed pregnancy was included in the analysis and pregnancy was the unit of analysis in all statistical testing. Pregnancies to the same woman were accounted for with generalized estimating equations and robust variance estimates to adjust for their lack of independence. Descriptive statistics were calculated by preterm status but no significance testing was conducted. To study the acute effect of air pollution on preterm birth, we performed a conditional logistic regression for each gestational week from 23–36, conditioning on women being at risk for delivery at that week (i.e., not previously delivered). We then compared exposure among deliveries at that week versus the same gestational week of exposure for all ongoing pregnancies. This is akin to a fetuses-at-risk approach which employs the idea of discrete-time survival analysis, but we fit saturated regression models by fully stratifying on the weeks of delivery. For these analyses, the risk estimate is interpreted as the odds of preterm delivery in a particular gestational week when exposure to the pollutant increases by one-IQR during that week. This interpretation is analogous to an “instantaneous risk ratio” in a survival analysis.

We also conducted analyses to examine the marginal probability of preterm birth (both <34 and <37 weeks) in association with ambient concentrations of each air pollutant for longer, more chronic exposure periods. Preliminary results of analyses of each gestational week from 1 to 28 suggested a change in risk over time that was well captured with equal division of the first two trimesters into 7-week increments (1–7; 8–14; 15–21; and 22–28). We also examined a three-month preconception window, the last six weeks of pregnancy and the total pregnancy. In contrast to the fetus-at-risk type of analyses, these logistic regressions estimated the marginal increase in the odds of preterm birth (or early preterm birth), per IQR increase in air pollution within a specific exposure window. As sensitivity analyses, risks

associated with peak weekly concentration during each of the 7-week windows were also estimated.

Odds ratios (ORs) and 95% confidence intervals for each week of gestation 23 to 36 and for dichotomous preterm birth outcomes (<34 weeks, <37 weeks) were estimated using logistic regression. Robust standard errors and generalized estimating equations were used to account for multiple births by the same women. Crude, site-adjusted models were generally similar to fully adjusted models and only adjusted results are shown. Interactions between maternal asthma and each pollutant were included in the models to test for effect modification. Odds ratios for women with and without asthma are calculated from the same model based on the interaction between maternal asthma status and each pollutant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.0.2. This study also utilized the high-performance computational capabilities of the Biowulf Linux cluster at the National Institutes of Health, Bethesda, MD. (<http://biowulf.nih.gov>). In consideration of the multiple time-windows and pollutants tested, we also evaluated the potential for false discovery among our findings using the method of Benjamini and Hochberg (35).

## Results

Preterm birth occurred in 11.7% of singleton deliveries (Table 1) and 33.6% of those deliveries were early preterm births (<34 weeks). As anticipated, preterm birth occurred more frequently among women who were Black, at the extremes of maternal age, single, had public insurance, smoked or drank alcohol during pregnancy and among women with chronic comorbid conditions prior to pregnancy. Women with asthma were more likely to deliver preterm, both early and overall.

Examining acute effects for each week of gestation (Figure 2), we found significant differences in preterm birth risk by asthma status that were fairly sporadic early in gestation with a significant increased risk for asthmatics at week 23 with NO<sub>x</sub> exposure, week 26 with PM<sub>2.5</sub>, and week 29 with NO<sub>x</sub>, PM<sub>2.5</sub> and PM<sub>10</sub>. At week 34, the acute risk for asthmatics is increased with exposure to NO<sub>x</sub> and SO<sub>2</sub> but decreased for O<sub>3</sub> compared to non-asthmatics. Asthmatics had significantly higher risk for preterm birth at week 35 associated with NO<sub>x</sub> exposure and at week 36 with increased CO and SO<sub>2</sub>. When we apply a correction for false discovery, significant interactions with maternal asthma remained for NO<sub>x</sub> at week 35 and for PM<sub>2.5</sub> at week 29. During some weeks where interaction terms were not significant at p<0.05 level, we also observed significantly elevated risk among asthmatic women. Regardless of significant interaction, the point estimates for preterm birth among asthmatic women are significantly elevated for PM<sub>2.5</sub> (weeks 26, 28 and 29), for PM<sub>10</sub> (weeks 28 and 36), for O<sub>3</sub> (week 33), for SO<sub>2</sub> (week 34 and 36), and elevated for CO in week 36 but inverse in week 30 (Supplemental Table 2). For non-asthmatics, inverse associations were more common and risks were seen only in relation to O<sub>3</sub> (weeks 23, 26, 27, and 28) and PM<sub>10</sub> (week 25) exposure.

For longer, more chronic exposure, results for seven-week averages (four windows: weeks 1–7, 8–14, 15–21 and 22–28), the last six-weeks of pregnancy and the broader preconception (3-month) and whole pregnancy windows are reported in Table 2.

With the exception of O<sub>3</sub>, most risk estimates were higher among asthmatic women for all windows studied. Preconception, both CO and NO<sub>x</sub> effects were higher among asthmatics with significant elevations of 12% in total preterm after CO exposure and 28–29% for total and early preterm after NO<sub>x</sub> exposure. In the first seven weeks of pregnancy, exposure to ambient concentrations of CO was associated with 8% higher total preterm risk for asthmatics (null for non-asthmatics) and NO<sub>x</sub> was associated with higher risk among asthmatics (22% increase for early preterm birth and 13% for total preterm births) while risk estimates for non-asthmatics were substantially lower (1–3% increased risk). Risks for asthmatics were lower after O<sub>3</sub> exposure during gestational weeks 8–21 and significant increased risks were observed for non-asthmatics in several windows for both total and early preterm birth. During the last six weeks of pregnancy, we observed statistically significant interaction between maternal asthma and CO, NO<sub>x</sub>, PM<sub>10</sub>, PM<sub>2.5</sub> and SO<sub>2</sub> but only the PM<sub>10</sub> estimate was significantly elevated for asthmatic mothers (9% increased risk compared to 1% for total preterm and 13% compared to null for early preterm).

After correction for potential false discovery, asthmatics remained at significantly higher risk for early preterm birth after exposure to NO<sub>x</sub> during nearly all time windows studied and for total preterm risk the interaction for NO<sub>x</sub> remained significant for preconception, the first seven weeks of pregnancy, the last six weeks of pregnancy and the whole pregnancy average. In addition, exposure to both PM<sub>10</sub> and PM<sub>2.5</sub> in the last six weeks of pregnancy was associated with higher risk among asthmatics for early preterm birth after false discovery correction.

## Discussion

In this large, contemporary obstetric cohort, we observed a pattern of associations that suggested preterm birth risk was higher among asthmatics exposed to most criteria air pollutants compared to non-asthmatics. Examining exposure in the last completed week for preterm births compared to ongoing pregnancies at the same week, we found significant interactions with higher risk for asthmatic mothers associated with NO<sub>x</sub>, CO, PM<sub>2.5</sub>, PM<sub>10</sub> and SO<sub>2</sub>. Only O<sub>3</sub> was associated with lower preterm birth risk among asthmatics.

Asthmatic women also appear to be particularly susceptible to early exposure to CO (8% higher risk), NO<sub>x</sub> (13% higher risk), PM<sub>10</sub> (8% higher risk) and PM<sub>2.5</sub> (8% higher risk) and late pregnancy exposure to PM<sub>10</sub> (9% higher risk) whereas O<sub>3</sub> exposure appears to increase risk in non-asthmatics.

Early preterm birth is less common, occurring in approximately 4% of singleton deliveries, but it is associated with greater neonatal mortality and substantial severe morbidity (36). Few prior studies have had sufficient power to examine this important group of cases (15) in relation to air pollution. Although most of our results were similar for both early and total preterm births overall, the risk estimates for women with asthma were somewhat higher for early preterm birth, particularly for NO<sub>x</sub> in weeks 1–7 (OR= 1.22 versus 1.13 for total

preterm) and for the PM<sub>10</sub> whole pregnancy average (OR=1.11 versus 1.05 for total preterm).

Our findings for very early pregnancy exposures to NO<sub>x</sub> and PM<sub>10</sub> associated with increased preterm birth risks are novel. The developing conceptus is highly susceptible to oxidative stress as are the processes involved in establishing utero-placental blood flow (37), and these mechanisms could underlie a higher risk for subsequent preterm birth. This time window was rarely examined in prior studies and it appears to be important. Consistent with our findings, a recent investigation of PM<sub>2.5</sub> also observed increased risk for preterm delivery associated with early pregnancy exposures in weeks 2–8 of gestation for both early preterm and total preterm births (15). Other studies of weekly data (14;16) have focused on the weeks prior to delivery rather than these early time windows. Our study is also novel in exploring a week-by-week risk estimation from 23 to 36 weeks comparing deliveries to exposure in ongoing pregnancies during the same gestational week.

First trimester exposure to SO<sub>2</sub> and particles has been associated with increased prematurity in the Czech Republic (10), while NO<sub>2</sub> was associated with preterm birth in Lithuania (11) but not in Spain (9). First trimester exposure to both CO and PM<sub>2.5</sub> increased preterm risk in California (8). In contrast, our findings for SO<sub>2</sub> and CO were null or inversely related to preterm birth risk among non-asthmatics across all of the windows we studied, but we did observe a 12% increased odds of preterm birth for preconception CO exposure among asthmatics.

Our study is the first to examine a preconception window, exploring the notion that these very early exposures may indicate a chronic inflammatory or vascular physiologic response that could lead to less than optimal conditions for implantation of the embryo and placentation – potential upstream factors related to preterm birth. In addition to the effect for CO mentioned above, we also observed an effect for NO<sub>x</sub> that is consistent with this notion but for the other criteria pollutants the preconception window risks were null or inverse. Chronic effects of air pollution are well known with respect to respiratory and cardiac effects (38), including increased mortality (39), and we have also observed a chronic effect of preconception exposure on other pregnancy outcomes (40;41). Collectively, these findings suggest further investigation of chronic preconception air pollutant exposure on pregnancy outcomes is warranted.

Our study has limitations, including the use of the hospital referral region as the geographic unit for our time-windows of exposure to estimate levels of ambient air pollutants. We therefore assumed that women lived and spent time in the catchment area of their delivery hospital. Averaging ambient pollutant concentrations across referral regions limits peaks and generally results in less variation than measurement at a residence which could lower our ability to observe a significant effect if one exists. On the other hand, women are likely to travel around their local area and a small regional average may provide a better proxy for exposure. We acknowledge that our exposure assessment strategy does not allow us to assess small area variation in exposure, although we note that our data come from across the US with broad geographic representation. Across various windows including the weekly analyses in Figure 2, particularly for non-asthmatics, we observe inverse associations

between pollutants and preterm birth. These findings are not biologically plausible in the sense that we do not anticipate that increases in air pollution exposure confer any protection, but they may be attributable in part to the correlations between pollutants. A functional analysis that included the temporal inter-correlation within pollutant across time windows (see Supplemental Table 3) did not appreciably change the estimates suggesting that within pollutant correlations were not responsible for the protective effects. On the other hand, O<sub>3</sub> is negatively correlated with other pollutants in our data (Supplemental Table 4) which may account for the difference in the pattern of outcomes for this secondary pollutant, including the lack of an association between ozone and preterm birth among asthmatics. While unmeasured confounding cannot be ruled out as an explanation for the inverse associations, we have controlled for a broad set of covariates and any such confounder is unlikely to be strongly related to maternal asthma. Finally, we recognize that although the intrapartum electronic medical records provide rich clinical data, they do not provide routine information unrelated to pregnancy such as asthma severity or treatment which could have impacted our findings. As such, we assume that our results reflect an “average” asthma patient’s experience and that stronger effects for women with severe or uncontrolled asthma are possible.

The strengths of our study include detailed exposure models which accounted for weather and both temporal and spatial dispersion with multiple sites across the US over an 8-year period. Preliminary models that also adjusted for season found nearly identical results for shorter time windows with some attenuation of findings for whole pregnancy suggesting that larger seasonal trends were not a major factor, likely due to the geographic dispersion of study sites. The evaluation of our model demonstrated superior performance in estimation of ambient pollutant levels compared with several other strategies, including observed monitor data (34). We examined a broad range of exposure windows given that there is no consensus on which windows are most important for preterm delivery risk. We recognize that this approach may lead to some chance findings due to multiple testing. While adjustment for multiple comparisons might be too restrictive in a novel exploration (42) where further research should be encouraged to confirm or refute potential chance findings, we applied a false-discovery correction to our findings (35). All of the interactions we observed with NO<sub>x</sub> remain significant after correction for multiple comparisons as do the interactions between maternal asthma and particle exposure in the last six weeks of pregnancy and early preterm birth. The large clinical database allowed us to control for detailed data on covariates that are not available in administrative sources such as birth certificates or insurance data. Notably, our findings for women with asthma suggest that they may be a vulnerable subpopulation with respect to air pollution exposure.

## Conclusions

Women with asthma have higher risks for preterm birth after acute exposure to most criteria air pollutants both early (weeks 23, 26 and 29) and later in gestation (weeks 34–36). Preconception and the first weeks of pregnancy appear to be important windows of susceptibility for preterm birth risk with respect to CO, NO<sub>x</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> exposure. Risks associated with O<sub>3</sub> appear higher later in gestation and are increased 16% for early preterm and 8% for total preterm in relation to whole pregnancy exposure among non-



asthmatics. Women with asthma often have higher risk associated with air pollutant exposures and even after adjustment for potential false discovery due to multiple comparisons, we find significantly increased risks for asthmatics after exposure to NO<sub>x</sub> and particles.

Small increases in preterm birth risk associated with air pollution merit attention given that asthma is common in the obstetric population and these exposures are difficult to manage at the individual level.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding Source:** This research was supported by the Intramural Research Program of the National Institutes of Health, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), including funding for the Consortium on Safe Labor (Contract No. HHSN267200603425C) and the Air Quality and Reproductive Health Study (Contract No. HHSN275200800002I, Task Order No. HHSN27500008). This paper has been cleared for publication by the NICHD but the funding source had no role in the design, analysis, interpretation or writing of the manuscript.

Institutions involved in the Consortium on Safe Labor include, in alphabetical order: Baystate Medical Center, Springfield, MA; Cedars-Sinai Medical Center Burnes Allen Research Center, Los Angeles, CA; Christiana Care Health System, Newark, DE; Georgetown University Hospital, MedStar Health, Washington, DC; Indiana University Clarian Health, Indianapolis, IN; Intermountain Healthcare and the University of Utah, Salt Lake City, Utah; Maimonides Medical Center, Brooklyn, NY; MetroHealth Medical Center, Cleveland, OH.; Summa Health System, Akron City Hospital, Akron, OH; The Emmes Corporation, Rockville MD (Data Coordinating Center); University of Illinois at Chicago, Chicago, IL; University of Miami, Miami, FL; and University of Texas Health Science Center at Houston, Houston, Texas.

The authors also acknowledge the expert programming support provided by Dr. Yeyi Zhu in the revisions for this manuscript.

## Abbreviations

CO	carbon monoxide
IQR	Interquartile range
O <sub>3</sub>	Ozone
PM <sub>10</sub>	particulate matter 10 microns
PM <sub>2.5</sub>	particulate matter 2.5 microns
SO <sub>2</sub>	sulfur dioxide

## References

1. Ferguson KK, O'Neill MS, Meeker JD. Environmental contaminant exposures and preterm birth: a comprehensive review. *J Toxicol Environ Health B Crit Rev.* 2013; 16(2):69–113. [PubMed: 23682677]
2. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. *Environ Res.* 2012

3. Shah PS, Balkhair T. Air pollution and birth outcomes: a systematic review. *Environ Int*. 2011; 37(2):498–516. [PubMed: 21112090]
4. Sapkota A, Chekilowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Qual Atmos Health*. 2012 Nov 23.5:369–81. 2012. Ref Type: Electronic Citation.
5. Nieuwenhuijsen MJ, Davvand P, Grellier J, Martinez D, Vrijheid M. Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. *Environ Health*. 2013; 12:6. [PubMed: 23320899]
6. Chang HH, Warren JL, Darrow LA, Reich BJ, Waller LA. Assessment of critical exposure and outcome windows in time-to-event analysis with application to air pollution and preterm birth study. *Biostatistics*. 2015
7. Xu X, Ding H, Wang X. Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study. *Arch Environ Health*. 1995; 50(6):407–15. [PubMed: 8572718]
8. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *Am J Epidemiol*. 2007; 166(9):1045–52. [PubMed: 17675655]
9. Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iniguez C. Preterm birth and exposure to air pollutants during pregnancy. *Environ Res*. 2010; 110(8):778–85. [PubMed: 20932516]
10. Bobak M. Outdoor air pollution, low birth weight, and prematurity. *Environ Health Perspect*. 2000; 108(2):173–6. [PubMed: 10656859]
11. Maroziene L, Grazuleviciene R. Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study. *Environ Health*. 2002; 1(1):6. [PubMed: 12495448]
12. Ballester F, Estarlich M, Iniguez C, Llop S, Ramon R, Esplugues A, et al. Air pollution exposure during pregnancy and reduced birth size: a prospective birth cohort study in Valencia, Spain. *Environ Health*. 2010; 9:6. [PubMed: 20113501]
13. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ Health Perspect*. 2003; 111(14): 1773–8. [PubMed: 14594630]
14. Sagiv SK, Mendola P, Loomis D, Herring AH, Neas LM, Savitz DA, et al. A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997–2001. *Environ Health Perspect*. 2005; 113(5):602–6. [PubMed: 15866770]
15. Rappazzo KM, Daniels JL, Messer LC, Poole C, Lobdell DT. Exposure to Fine Particulate Matter during Pregnancy and Risk of Preterm Birth among Women in New Jersey, Ohio, and Pennsylvania, 2000–2005. *Environ Health Perspect*. 2014
16. Darrow LA, Klein M, Flanders WD, Waller LA, Correa A, Marcus M, et al. Ambient air pollution and preterm birth: a time-series analysis. *Epidemiology*. 2009; 20(5):689–98. [PubMed: 19478670]
17. Gehring U, van EM, Dijkema MB, van der Wal MF, Fischer P, Brunekreef B. Traffic-related air pollution and pregnancy outcomes in the Dutch ABCD birth cohort study. *Occup Environ Med*. 2011; 68(1):36–43. [PubMed: 20798012]
18. Gehring U, Wijga AH, Fischer P, de Jongste JC, Kerkhof M, Koppelman GH, et al. Traffic-related air pollution, preterm birth and term birth weight in the PIAMA birth cohort study. *Environ Res*. 2011; 111(1):125–35. [PubMed: 21067713]
19. Ritz B, Yu F, Chapa G, Fruin S. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. *Epidemiology*. 2000; 11(5):502–11. [PubMed: 10955401]
20. Woodruff TJ, Parker JD, Darrow LA, Slama R, Bell ML, Choi H, et al. Methodological issues in studies of air pollution and reproductive health. *Environ Res*. 2009; 109(3):311–20. [PubMed: 19215915]
21. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, et al. Meeting report: atmospheric pollution and human reproduction. *Environ Health Perspect*. 2008; 116(6): 791–8. [PubMed: 18560536]

22. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet*. 2014; 383(9928):1581–92. [PubMed: 24792855]
23. Akinbami, LJ.; Moorman, JE.; Bailey, C.; Zahran, HS.; King, M.; Johnson, CA., et al. Trends in asthma prevalence, health care use and mortality in the United States, 2001–2010. National Center for Health Statistics; Hyattsville MD: 2012. NCHS data brief, no 94 . 5-20-2012Ref Type: Electronic Citation
24. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG*. 2011; 118(11):1314–23. [PubMed: 21749633]
25. Mendola P, Laughon SK, Mannisto TI, Leishear K, Reddy UM, Chen Z, et al. Obstetric complications among US women with asthma. *Am J Obstet Gynecol*. 2013; 208(2):127–8. [PubMed: 23159695]
26. Olsson D, Mogren I, Forsberg B. Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. *BMJ Open*. 2013; 3(2)
27. Martinelli N, Olivieri O, Girelli D. Air particulate matter and cardiovascular disease: a narrative review. *Eur J Intern Med*. 2013; 24(4):295–302. [PubMed: 23647842]
28. Huang YC, Ghio AJ. Controlled human exposures to ambient pollutant particles in susceptible populations. *Environ Health*. 2009; 8:33. [PubMed: 19630984]
29. Institute for Health Metrics and Evaluation. Global burden of disease. Institute for Health Metrics and Evaluation, University of Washington; Mar 20. 2015 Ref Type: Electronic Citation
30. Zhang J, Troendle J, Reddy UM, Laughon SK, Branch DW, Burkman R, et al. Contemporary cesarean delivery practice in the United States. *Am J Obstet Gynecol*. 2010; 203(4):326. [PubMed: 20708166]
31. Mendola P, Mannisto TI, Leishear K, Reddy UM, Chen Z, Laughon SK. Neonatal health of infants born to mothers with asthma. *J Allergy Clin Immunol*. 2014; 133(1):85–90. [PubMed: 23916153]
32. Byun D, Shere KL. Review of the governing equations, computational algorithms, and other components of the Models-3 Community Multiscale Air Quality (CMAQ) modeling system. *Appl Mech Rev*. 2006; 59:51–78.
33. The Dartmouth Institute for Health Policy and Clinical Practice. Dartmouth Atlas Project. Mar 20. 2015 The Dartmouth Atlas of Care.
34. Chen G, Li J, Ying Q, Sherman S, Perkins N, Rajeshwari S, et al. Evaluation of observation-fused regional air quality model results for population air pollution exposure estimation. *Sci Total Environ*. 2014; 485–486:563–74.
35. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Statist Soc B*. 1995; 57(1):289–300.
36. Ancel PY, Goffinet F, Kuhn P, Langer B, Matis J, Hernandez X, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr*. 2015; 169(3):230–8. [PubMed: 25621457]
37. Al-Gubory KH, Fowler PA, Garrel C. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. *Int J Biochem Cell Biol*. 2010; 42(10):1634–50. [PubMed: 20601089]
38. Mannucci PM, Harari S, Martinelli I, Franchini M. Effects on health of air pollution: a narrative review. *Intern Emerg Med*. 2015
39. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: an extended follow-up of the Harvard Six Cities study from 1974 to 2009. *Environ Health Perspect*. 2012; 120(7):965–70. [PubMed: 22456598]
40. Robledo CA, Mendola P, Yeung E, Mannisto T, Sundaram R, Liu D, et al. Preconception and early pregnancy air pollution exposures and risk of gestational diabetes mellitus. *Environ Res*. 2015; 137:316–22. [PubMed: 25601734]
41. Zhu Y, Zhang C, Liu D, Grantz KL, Wallace M, Mendola P. Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. *Environ Res*. 2015; 140:714–20. [PubMed: 26099933]
42. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990; 1(1):43–6. [PubMed: 2081237]

### **Clinical Implications**

Pregnant women with asthma had significantly higher risk of preterm birth compared to non-asthmatics after both chronic and short-term exposure to many air pollutants, particularly carbon monoxide and nitrogen oxides.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Capsule Summary**

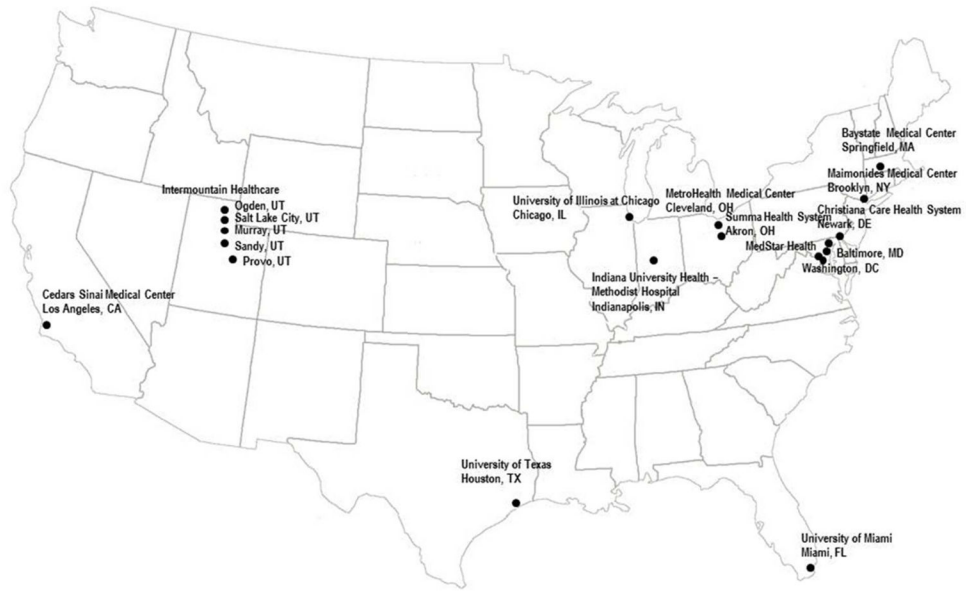
In a large U.S. obstetric cohort, asthmatic mothers were more likely to deliver preterm after air pollution exposure, particularly carbon monoxide and nitrogen oxides preconception, in early gestation and in the weeks prior to delivery.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript



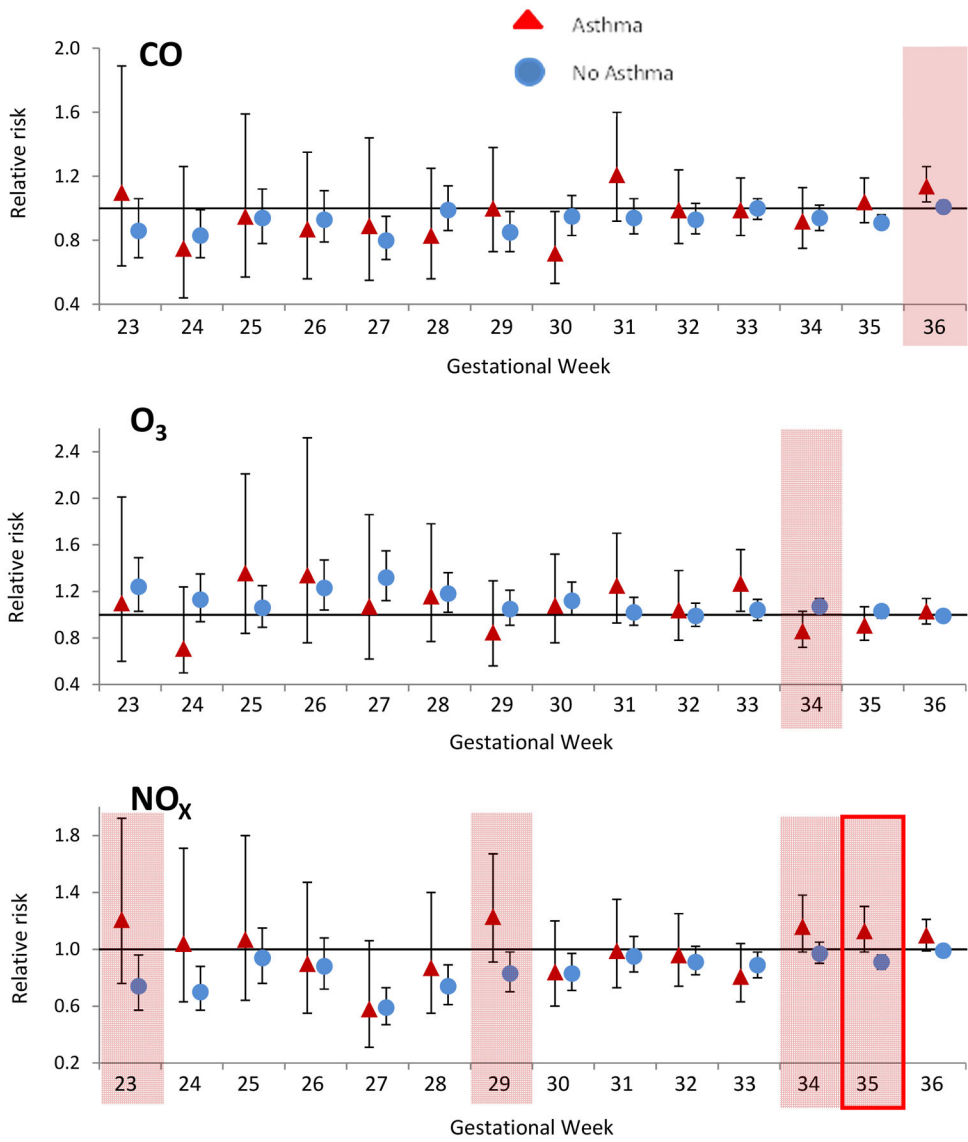
**Figure 1.**  
Study site locations.

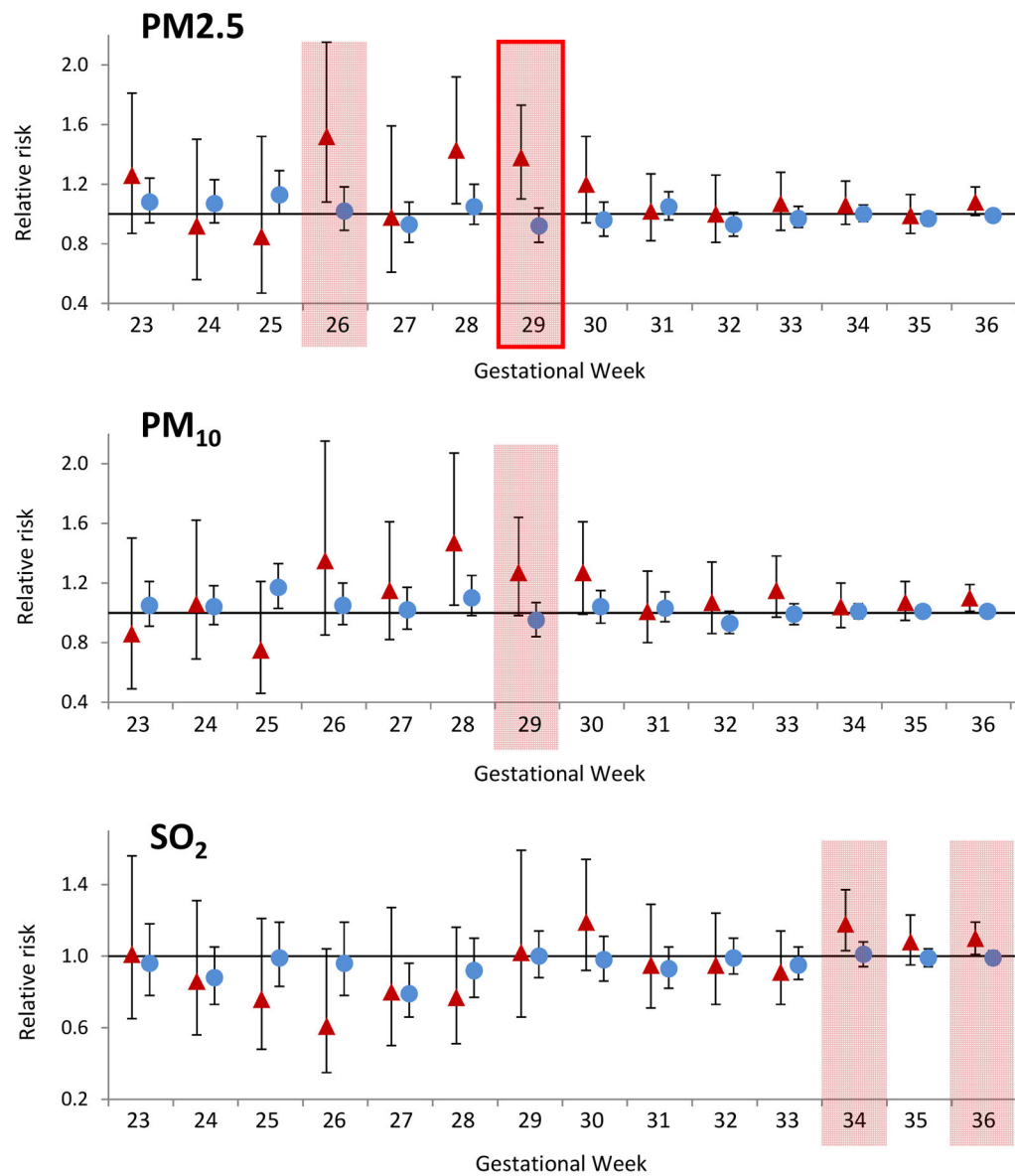
Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript



**Figure 2.**

Risk of preterm birth associated with air pollutants by asthma status for each week of gestation from 23 to 36. Significant interactions with asthma are designated by highlighted bars, outlined bars denote significance after false discovery correction.



Table 1

Study population characteristics by preterm status (N=223,502).

	Early preterm birth <34 weeks n=8,772		Total Preterm Birth <37 weeks n=26,144		Term birth 37 weeks n=197,358	
	n	%	n	%	n	%
<b>Race/ethnicity</b>						
White	2,946	33.6	10,590	40.5	100,010	50.7
Black	3,333	38.0	8,464	32.4	41,818	21.2
Hispanic	1,552	17.7	4,575	17.5	34,253	17.4
Asian/Pacific Islander	200	2.3	771	3.0	8,409	4.3
Other Race	311	3.6	725	2.8	4,506	2.3
Unknown	430	4.9	1,019	3.9	8,362	4.2
<b>Age</b>						
<20	1,125	12.9	3021	11.6	17,680	9.0
20–24	2,244	25.6	6645	24.5	49,977	25.4
25–29	1,993	22.8	6533	25.0	55,714	28.3
30–34	1,831	20.9	5545	21.2	44,625	22.6
35	1,558	17.8	4363	16.7	29,091	14.8
Missing	21	0.2	37	0.1	271	0.1
<b>Pre-pregnancy BMI</b>						
Underweight	282	3.2	985	3.8	6,995	3.5
Normal weight	2,193	25.0	7,770	29.7	71,243	36.1
Over weight	1,160	13.2	3,693	14.1	29,896	15.2
Obese	1,236	14.1	3,668	14.0	24,232	12.3
Missing	3,901	44.5	10,028	38.4	64,992	32.9
<b>Parity</b>						
Nulliparous	3,860	44.0	10525	40.3	78,710	39.9
Primiparous	2,248	25.6	7172	27.4	61,148	31.0
Multiparous	2,661	30.3	8447	32.3	57,500	29.1
<b>Marital Status</b>						
Married	3,804	43.7	12,737	48.7	118,524	60.1
Divorced/Widowed	176	2.0	579	2.2	2,963	1.5

	Early preterm birth <34 weeks n=8,772		Total Preterm Birth <37 weeks n=26,144		Term birth 37 weeks n=197,358	
	n	%	n	%	n	%
Single	4,388	50.0	11,840	45.3	69,630	35.3
Unknown	404	4.6	988	3.8	6,241	3.2
<b>Insurance status</b>						
Private	3,864	44.1	12,459	47.7	11,2498	57.0
Public/Government	3,933	44.8	10,697	40.9	61,505	31.2
Self-pay/other	166	1.9	459	1.8	2,522	1.3
Unknown	809	9.2	2,528	9.7	20,833	10.6
<b>Smoked during pregnancy</b>	1,003	11.4	2,668	10.2	12,265	6.2
<b>Used alcohol during pregnancy</b>	284	3.2	668	2.6	3,423	1.7
<b>Asthma</b>	873	10.0	2,526	9.7	14,517	7.4
<b>Comorbidity</b>	1,023	11.7	2,845	10.9	11,281	5.7

BMI = body mass index, (weight in kilograms/height in meters<sup>2</sup>).

Comorbidity = chronic hypertension, diabetes, thyroid disease and HIV.

**Table 2**

Adjusted odds ratios and 95% confidence intervals for early preterm birth and total preterm birth for an interquartile range increase in criteria air pollutants by asthma status.<sup>a,b</sup>

	Early preterm birth (<34 weeks)				Total Preterm birth (<37 weeks)							
	Asthma		No asthma		Asthma		No asthma					
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI				
<b>CO</b>												
3 months preconception	1.10	0.94	1.30	1.04	0.98	1.11	<b>1.12</b>	<b>1.01</b>	<b>1.23</b>	<b>1.01</b>	<b>0.97</b>	<b>1.04</b>
Weeks 1–7	1.10	0.98	1.23	1.01	0.97	1.05	<b>1.08</b>	<b>1.00</b>	<b>1.15</b>	<b>1.00</b>	<b>0.97</b>	<b>1.02</b>
Weeks 8–14	<b>1.06</b>	<b>0.95</b>	<b>1.18</b>	<b>0.94</b>	<b>0.90</b>	<b>0.98</b>	1.00	0.94	1.07	0.96	0.94	0.98
Weeks 15–21	<b>1.05</b>	<b>0.93</b>	<b>1.17</b>	<b>0.93</b>	<b>0.89</b>	<b>0.97</b>	0.99	0.93	1.06	0.95	0.93	0.98
Weeks 22–28	0.91	0.81	1.02	0.85	0.82	0.89	0.97	0.91	1.04	0.94	0.92	0.96
Last 6 weeks of pregnancy	0.94	0.85	1.05	0.90	0.87	0.94	<b>1.00</b>	<b>0.93</b>	<b>1.07</b>	<b>0.92</b>	<b>0.90</b>	<b>0.94</b>
Whole pregnancy	1.03	0.92	1.15	0.92	0.88	0.97	1.04	0.97	1.11	0.98	0.95	1.00
<b>NO<sub>x</sub></b>												
3 months preconception	1.29	1.06	1.57	1.09	0.99	1.20	<b>1.28</b>	<b>1.13</b>	<b>1.45</b>	<b>1.08</b>	<b>1.02</b>	<b>1.14</b>
Weeks 1–7	<b>1.22</b>	<b>1.08</b>	<b>1.37</b>	<b>1.01</b>	<b>0.96</b>	<b>1.07</b>	<b>1.13</b>	<b>1.05</b>	<b>1.22</b>	<b>1.03</b>	<b>1.00</b>	<b>1.06</b>
Weeks 8–14	<b>1.11</b>	<b>0.98</b>	<b>1.25</b>	<b>0.91</b>	<b>0.86</b>	<b>0.96</b>	1.03	0.95	1.11	0.96	0.93	0.99
Weeks 15–21	<b>1.05</b>	<b>0.93</b>	<b>1.20</b>	<b>0.85</b>	<b>0.81</b>	<b>0.90</b>	1.00	0.92	1.08	0.94	0.91	0.97
Weeks 22–28	<b>0.92</b>	<b>0.81</b>	<b>1.06</b>	<b>0.80</b>	<b>0.75</b>	<b>0.85</b>	0.99	0.92	1.07	0.93	0.90	0.96
Last 6 weeks of pregnancy	<b>1.02</b>	<b>0.91</b>	<b>1.15</b>	<b>0.81</b>	<b>0.78</b>	<b>0.84</b>	<b>1.02</b>	<b>0.95</b>	<b>1.10</b>	<b>0.85</b>	<b>0.83</b>	<b>0.87</b>
Whole pregnancy	<b>1.02</b>	<b>0.90</b>	<b>1.15</b>	<b>0.84</b>	<b>0.79</b>	<b>0.90</b>	<b>1.06</b>	<b>0.99</b>	<b>1.14</b>	<b>0.98</b>	<b>0.94</b>	<b>1.01</b>
<b>O<sub>3</sub></b>												
3 months preconception	0.81	0.71	0.93	0.90	0.85	0.95	0.92	0.85	1.00	0.95	0.91	0.98
Weeks 1–7	0.90	0.80	1.00	1.00	0.96	1.04	0.97	0.91	1.04	0.98	0.96	1.00
Weeks 8–14	<b>0.95</b>	<b>0.85</b>	<b>1.07</b>	<b>1.10</b>	<b>1.05</b>	<b>1.14</b>	1.03	0.95	1.10	1.04	1.01	1.06
Weeks 15–21	<b>1.00</b>	<b>0.89</b>	<b>1.13</b>	<b>1.16</b>	<b>1.11</b>	<b>1.21</b>	1.05	0.98	1.13	1.06	1.04	1.09
Weeks 22–28	0.99	0.88	1.12	1.05	1.00	1.09	0.99	0.92	1.07	1.03	1.00	1.06
Last 6 weeks of pregnancy	1.00	0.89	1.11	1.01	0.98	1.05	0.97	0.91	1.03	1.01	0.99	1.04
Whole pregnancy	1.00	0.83	1.20	1.16	1.08	1.25	1.02	0.91	1.15	1.08	1.03	1.13

	Early preterm birth (<34 weeks)				Total Preterm birth (<37 weeks)							
	Asthma		No asthma		Asthma		No asthma					
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI				
<b>PM<sub>10</sub></b>												
3 months preconception	<b>0.97</b>	<b>0.82</b>	<b>1.16</b>	<b>0.81</b>	<b>0.76</b>	<b>0.87</b>	1.00	0.90	1.11	0.93	0.89	0.96
Weeks 1–7	1.08	0.98	1.19	1.01	0.97	1.04	1.08	1.02	1.15	1.04	1.02	1.07
Weeks 8–14	1.02	0.92	1.13	0.99	0.96	1.03	1.02	0.96	1.08	0.98	0.96	1.00
Weeks 15–21	1.05	0.95	1.15	1.01	0.98	1.04	1.03	0.98	1.09	1.00	0.98	1.02
Weeks 22–28	1.03	0.94	1.13	0.95	0.92	0.98	1.02	0.97	1.08	1.00	0.98	1.02
Last 6 weeks of pregnancy	<b>1.13</b>	<b>1.03</b>	<b>1.24</b>	<b>0.98</b>	<b>0.85</b>	<b>1.01</b>	<b>1.09</b>	<b>1.03</b>	<b>1.15</b>	<b>1.01</b>	<b>0.99</b>	<b>1.03</b>
Whole pregnancy	1.09	1.00	1.20	1.03	0.99	1.06	1.05	0.99	1.10	1.02	1.00	1.04
<b>PM<sub>2.5</sub></b>												
3 months preconception	0.77	0.61	0.96	0.77	0.70	0.85	0.96	0.84	1.09	0.90	0.85	0.95
Weeks 1–7	1.11	0.99	1.24	1.04	0.99	1.08	1.08	1.01	1.15	1.04	1.02	1.07
Weeks 8–14	1.02	0.92	1.14	0.97	0.93	1.01	1.02	0.95	1.08	0.97	0.94	0.99
Weeks 15–21	1.05	0.95	1.16	1.01	0.97	1.04	0.98	0.92	1.04	0.97	0.95	0.99
Weeks 22–28	0.99	0.90	1.10	0.92	0.88	0.96	1.00	0.94	1.06	0.99	0.97	1.01
Last 6 weeks of pregnancy	<b>1.03</b>	<b>0.93</b>	<b>1.15</b>	<b>0.88</b>	<b>0.85</b>	<b>0.91</b>	<b>0.99</b>	<b>0.93</b>	<b>1.06</b>	<b>0.91</b>	<b>0.89</b>	<b>0.93</b>
Whole pregnancy	1.11	1.01	1.22	1.02	0.98	1.05	1.05	0.99	1.11	1.01	0.99	1.03
<b>SO<sub>2</sub></b>												
3 months preconception	0.74	0.61	0.91	0.85	0.78	0.92	0.93	0.84	1.04	0.92	0.87	0.96
Weeks 1–7	1.00	0.89	1.13	0.97	0.92	1.02	0.99	0.92	1.06	0.98	0.95	1.01
Weeks 8–14	0.90	0.78	1.04	0.88	0.83	0.92	0.96	0.89	1.03	0.95	0.92	0.98
Weeks 15–21	0.89	0.78	1.02	0.88	0.83	0.93	0.95	0.88	1.02	0.95	0.92	0.98
Weeks 22–28	0.85	0.75	0.98	0.89	0.84	0.94	0.98	0.91	1.06	0.96	0.93	0.99
Last 6 weeks of pregnancy	0.82	0.73	0.92	0.93	0.80	0.86	<b>0.94</b>	<b>0.88</b>	<b>1.00</b>	<b>0.88</b>	<b>0.86</b>	<b>0.89</b>
Whole pregnancy	0.90	0.80	1.01	0.88	0.83	0.92	0.96	0.90	1.02	0.95	0.92	0.98

<sup>a</sup>Model controlled for maternal age, race, pre-pregnancy BMI, smoking and alcohol use, study site, parity, insurance status, marital

<sup>b</sup>Estimates in bold indicate significant interaction between asthma and pollutant.

Shaded blocks indicate significant findings after false discovery correction.