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Air pollution exposure and preeclampsia among US women with and without asthma

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Abstract

Maternal asthma and air pollutants have been independently associated with preeclampsia but rarely studied together. Our objective was to comprehensively evaluate preeclampsia risk based on the interaction of maternal asthma and air pollutants. Preeclampsia and asthma diagnoses, demographic and clinical data came from electronic medical records for 210,508 singleton deliveries. Modified Community Multiscale Air Quality models estimated preconception, first and second trimester and whole pregnancy exposure to: particulate matter (PM) < 2.5 and < 10 μm, ozone, nitrogen oxides (NO_x), sulfur dioxide (SO_2) and carbon monoxide (CO); $PM_{2.5}$ constituents; volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs). Asthma-pollutant interaction adjusted relative risks (RR) and 95% confidence intervals (CI) for preeclampsia were calculated by interquartile range for criteria pollutants and high exposure (≥ 75th percentile) for PAHs and VOCs. Asthmatics had higher risk associated with first trimester NO_x and SO_2 and whole pregnancy elemental carbon (EC) exposure than non-asthmatics, but only EC significantly increased risk (RR=1.11, CI:1.03–1.21). Asthmatics also had a 10% increased risk associated with second trimester CO. Significant interactions were observed for nearly all VOCs and asthmatics had higher risk during all time windows for benzene, ethylbenzene, m-xylene, o-xylene, p-xylene and toluene while most PAHs did not increase risk.

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Compliance with ethical standards

All participating institutions (noted in the acknowledgements) have Institutional Review Board approval. Data are anonymous with no individual identifying information included and no individual consent was required.

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.04.004.

Keywords

Preeclampsia; Pregnancy; Hypertension; Asthma; Air pollution

1. Introduction

Ambient air pollution appears to increase the risk for hypertensive disorders of pregnancy (Pedersen et al., 2014). Preeclampsia is new-onset hypertension, often with proteinuria, diagnosed after 20 weeks of gestation. It is a serious complication of pregnancy associated with preterm birth as well as substantial morbidity and mortality in mothers and infants (Hutcheon et al., 2011). Recent meta-analyses found significant increased risks for preeclampsia associated with particulate matter < 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and traffic exposures, but no significant increased risk associated with nitrogen oxides (NO_x), particulate matter < 10 μm (PM_{10}), carbon monoxide (CO) or ozone (O_3) (Pedersen et al., 2014). Maternal asthma has also been associated with preeclampsia in a recent meta-analysis (Murphy et al., 2011), and in our data, we previously observed a 14% increase in the adjusted odds of preeclampsia in singleton pregnancies complicated by maternal asthma (Mendola et al., 2013).

Asthma is common among women of reproductive age (Moorman et al., 2012). While air pollution can exacerbate asthma (Guarnieri and Balmes, 2014), only one prior study examined the interaction of asthma and air pollutants, looking exclusively at first trimester exposure to NO_x and O_3. Olsson et al. (2013). This Swedish register-based study found no relation between preeclampsia and NO_x and no significant interactions for O_3 and asthma in the risk for preeclampsia. Our aim was to examine whether the relationships between preeclampsia and criteria air pollutant exposures as well as exposure to high levels of polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs) were different among women with and without asthma, for exposures preconception and throughout pregnancy, in a large contemporary U.S. obstetric cohort.

2. Materials and methods

2.1. Study population

Our study is based on a retrospective cohort of 228,438 births at ≥ 23 weeks gestation assembled using hospital delivery admission electronic medical records (both mother and neonate charts) from 12 centers (19 hospitals; 15 hospital referral regions) across the United States (Zhang et al., 2010). We excluded multi-fetal pregnancies (n=5053), pregnancies missing air quality data (n=10) or maternal age (n=307), women with chronic hypertension (n=4358) and superimposed preeclampsia (n=1889) because they were not at risk for new-onset hypertension. We also excluded women with gestational hypertension (n=6074) or eclampsia (n=239) to allow comparison of preeclampsia cases to a normotensive reference group. This resulted in an analytic sample of 210,508 singleton pregnancies among 192,687 women. Most women (175,700; 91.1%) contributed only one pregnancy. All participating institutions in the Consortium on Safe Labor, noted in the acknowledgements, received

institutional review board approval for the study. All records are anonymized and individual patient consent was not required.

2.2. Outcome and covariates

Both preeclampsia and maternal asthma diagnoses were indicated in the electronic records and/or in the maternal discharge summary using International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes. The specific gestational age at preeclampsia diagnosis was not available, but severity of preeclampsia was distinguished using ICD-9 codes (642.4: mild or unspecified preeclampsia; 642.5: severe preeclampsia). Asthma diagnosis was recorded in the medical record and/or in the discharge summary (ICD-9 code 493.0–493.9). Maternal age (continuous), race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other/Unknown), pre-pregnancy body mass index (BMI) category (underweight < 18.5, normal weight 18.5 to < 25, overweight 25 to < 30, obese ≥ 30, unknown), parity (nulliparous, primiparous, multiparous), marital status (married, divorced/widowed, single, unknown), insurance status (public, private, other, unknown), smoking and alcohol use during pregnancy (both yes/no) were all derived from the electronic medical record.

2.3. Exposure

We estimated air pollutant exposures, both for criteria pollutants and hazardous air toxics, using a modified version of the Community Multiscale Air Quality (CMAQ) model, which is based on a three-dimensional, regional air quality model developed by the U.S. Environmental Protection Agency (U.S. EPA). The model inputs weather data including hourly measures of temperature, relative humidity and wind characteristics as well as air pollutant emissions generated using the U.S. EPA National Emission Inventories. Hourly exposures were calculated over the entire continental U.S. for the years 2001–2010 in the Air Quality and Reproductive Health study which was completed in 2013 and described in detail elsewhere (Chen et al., 2014). Briefly, model estimates for criteria air pollutants: $PM_{2.5}$, PM_{10}, O_3, NOx, sulfur dioxide (SO_2) and CO were fused with monitor data from the US EPA Air Quality System to correct for measurement errors using inverse distance weighting to take advantage of measured data where they were available. Constituents of $PM_{2.5}$, polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs) were based on CMAQ model output since these pollutants are not routinely monitored. The final model demonstrated improved performance in comparison with four other exposure assessment strategies, including monitor data alone and raw CMAQ data (Chen et al., 2014).

Hourly exposure estimates were averaged across the delivery hospital referral region and weighted for population density to estimate windows of exposure for each pregnancy as a proxy for maternal residence and local mobility. The size of hospital referral regions ranged from 415 to 312,644 square kilometers. The preconception window was an average of 90 days prior to the last menstrual period which was calculated based on the best obstetrical estimate of gestational age. We also estimated the first and second trimester average (0 to < 14 gestational weeks and 14 to < 28 gestational weeks, respectively) and the whole pregnancy average. Since preeclampsia is diagnosed after 20 weeks by definition, the preconception and first trimester time windows will always precede diagnosis. Most

pregnancies also have a full second trimester window. We included the whole pregnancy time window to be comparable with other studies and because a preeclampsia diagnosis triggers a medically-indicated delivery at or near term and expectant management will often lead to delivery within 1–2 weeks (Magee et al., 2009; Koopmans et al., 2009). Accordingly, whole pregnancy might be considered a proxy of an average exposure until diagnosis.

2.4. Statistical analyses

Pregnancy was the unit of analysis in all statistical testing. Frequency distributions of pregnancies with and without asthma by preeclampsia status were calculated. Log linear models, with generalized estimating equations to account for multiple births to the same mother, were used to calculate the relative risk and 95% confidence intervals for preeclampsia. Interaction terms between maternal asthma and each pollutant were included to test the effect modification by asthma status. Interactions with a $p < 0.05$ were considered significant. Models were adjusted for site and covariates from the medical record including maternal age, race/ethnicity, pre-pregnancy body mass index, parity, marital status, insurance, smoking and alcohol use during pregnancy. Site-adjusted crude models were similar to fully adjusted models. Therefore, only fully adjusted models are presented. Criteria air pollutants (PM_{10}, $PM_{2.5}$, O_3, NO_x, SO_2, CO) and $PM_{2.5}$ constituents were analyzed in the continuous scale and relative risks were calculated for these pollutants based on the interquartile range (IQR; the difference between the 25th and 75th percentile; Supplemental Table 1). Since PAHs and VOCs were generally observed at very low levels and the model results were not fused with existing monitor data, we chose to dichotomize exposure at the 75th percentile to estimate risk associated with high exposure rather than assume a linear model.

Sensitivity analyses were conducted restricting the dataset to nulliparous women who are known to have higher preeclampsia risk. We also restricted the analyses to obese women only and to normal weight women only to assess the potential impact of maternal weight on our findings. Finally, we examined the subset of severe preeclampsia cases which may be less likely to be impacted by air quality. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

As anticipated, maternal asthma was more common in pregnancies with preeclampsia (9% versus 7%, Table 1). Women with preeclampsia were slightly younger, more likely to be black, have higher BMI, and to be nulliparous. Smoking was less common in pregnancies with preeclampsia for both asthmatics and non-asthmatics.

We observed significant interactions for NO_x and SO_2 in the first trimester and for elemental carbon in the whole pregnancy average, with higher risk estimates among asthmatics (Table 2). Risks were significantly elevated 11% for asthmatics in association with whole pregnancy elemental carbon exposure and 10% for second trimester CO exposure. Among non-asthmatics, significant risk reductions were observed for first trimester NO_x and SO_2 exposure, with elevated risks associated with elemental carbon and organic compounds in

the second trimester, sulfite particles in the first trimester and whole pregnancy dust particles.

The interaction of VOCs and asthma (Table 3) reveals a fairly consistent pattern of increased risk for asthmatics (6–70%) with significant interactions observed for most of the compounds studied in multiple windows. Significantly increased risks (13–70%) for asthmatics compared to non-asthmatics were seen in every time window studied for benzene, ethylbenzene, m-xylene, o-xylene, p-xylene, and toluene. Risk estimates tended to be higher for whole pregnancy average exposures for both asthmatics and non-asthmatics. No interaction was observed for methyl-tertiary butyl ether, sesquiterpene or styrene. Preeclampsia risk estimates were elevated for both asthmatics (39%) and non-asthmatics (15%) in relation to second trimester benzene exposure and whole pregnancy exposure increased risk for asthmatics only. Ethylbenzene increased preeclampsia risk in all time windows (23–70%) among asthmatics but only whole pregnancy exposure significantly increased risk for non-asthmatics. Cyclohexane increased risk for asthmatics in the first trimester (19%) and whole pregnancy for asthmatics (31%) and non-asthmatics (8%). N-hexane was associated with increased risk for asthmatics in the second trimester (28%) and whole pregnancy for asthmatics (54%) and non-asthmatics (28%). Methyl ethyl ketone increased risk 23–24% for all pregnancy windows only among women with asthma. For m-xylene and p-xylene, all windows had significantly elevated risks (20–62%) for asthmatics but only whole pregnancy exposure increased risk for non-asthmatics (25–33%). The pattern of preeclampsia risk was similar for o-xylene but the magnitude of increase was smaller than with the other xylene compounds. Propene increased risk only for asthmatics in the first trimester (15%) and after whole pregnancy exposure (17%). Sesquiterpene increased preeclampsia risk for asthmatics (16%) after first trimester exposure and after second trimester exposure in non-asthmatics (6%). Toluene in all pregnancy time windows increased risk among asthmatics (31–38%) but only increased preeclampsia risk in non-asthmatics after second trimester exposure (14%).

PAH exposure had less of an impact on preeclampsia risk overall and interactions with maternal asthma were less common (Table 4). Significant interactions were observed with preconception fluoranthene and most windows for naphthalene were associated with increased risk for asthmatics (11–21%) but no other compounds or windows differed by asthma status. Elevated preeclampsia risk was observed for non-asthmatics associated with acenaphthene second trimester and whole pregnancy exposure (6–7%) and for whole pregnancy acenaphthylene (9%). Preconception anthracene was associated with 5% increased preeclampsia risk in non-asthmatics. Preconception fluoranthene increased risk 15% for asthmatics and second trimester exposure increased risk 8% for non-asthmatics. Fluorene in the second trimester and whole pregnancy increased risk 7–8% for non-asthmatics. Naphthalene increased risk for asthmatics in the second trimester and whole pregnancy (21%) and whole pregnancy pyrene increased preeclampsia risk for non-asthmatics (7%).

Analyses restricted to nulliparous women, as well as those restricted by pre-pregnancy BMI status to normal weight only and obese women only, generally yielded similar results as the main analyses although with a loss of precision due to the smaller sample. Restriction to

severe preeclampsia cases attenuated the results and several inverse associations were observed (data not shown).

4. Discussion

We found first trimester exposure to NO_x and SO_2 and whole pregnancy elemental carbon were associated with higher risks of preeclampsia among asthmatic women compared to their non-asthmatic counterparts. SO_2 has not been previously studied in relation to preeclampsia alone, so our findings for this pollutant are novel. Most notably, nearly all the VOCs we studied were associated with increased risk of preeclampsia, with significantly higher risk in pregnancies complicated by maternal asthma. In our data, modeled VOC exposure among asthmatics was associated with increased preeclampsia risk up to 70%. In contrast, with the exception of naphthalene and fluoranthene, PAH exposures rarely interacted with maternal asthma in relation to preeclampsia risk, but some PAHs were associated with elevated risk in both groups.

A recent meta-analysis (Pedersen et al., 2014) found no significant effect of O_3, CO, PM_{10}, or NO_x on preeclampsia risk. Neither $PM_{2.5}$ nor NO_2 were associated with preeclampsia in a recent study of similar size based on vital records in New York City (Savitz et al., 2015). With regard to $PM_{2.5}$, all time windows studied were null in our analyses, in contrast to the 30% increased risk estimated by Pederson and colleagues (Pedersen et al., 2014) but consistent with the findings by Savitz and colleagues (Savitz et al., 2015). One prior paper that controlled for maternal asthma found a 4% increase in preeclampsia after first trimester exposure to ozone and no effect for NO_2 in a Swedish registry-based study (Olsson et al., 2013). In contrast, we observed no effect for ozone at any time window and no significant interaction with asthma, although our first trimester relative risk of 1.03 is similar to the risk estimates of 1.04–1.05 for ozone single-pollutant models reported by Olsson and colleagues (Olsson et al., 2013).

A study based on a hospital cohort in Pittsburgh found no significant effect on preeclampsia after first trimester exposure to $PM_{2.5}$ or ozone measured using space/time kriging to estimate zip code level exposures, although the point estimates were elevated (Lee et al., 2013). Land use regression models were used in Western Australia to estimate NO_2 as a marker for traffic (Pereira et al., 2013) with a 30% increase in preeclampsia observed with third trimester exposure and 12% increase with the whole pregnancy average. In Los Angeles and Orange County, California, line-source dispersion models to estimate whole pregnancy traffic exposures found a 33% increase in preeclampsia for NO_x and 42% increase in the highest quartile of $PM_{2.5}$ (Wu et al., 2009). Building on that study, the authors compared various exposure assessment methods and found some variation in risk by both location and model choice with significant effects for ozone in Orange County and CO in Los Angeles that were not consistently observed (Wu et al., 2011). CO has also been associated with protective effects in a large Ontario, Canada study that linked birth records to ambient monitoring data and observed a dose-response reduction in preeclampsia with a nearly 50% reduction in the highest quartile of exposure (Zhai et al., 2012). In the only other study that evaluated preconception time windows (Rudra et al., 2011), CO was associated with a two-fold increased risk of preeclampsia in Washington State but no effect was

observed for $PM_{2.5}$. We observed a significant increase in risk for asthmatics (RR = 1.10) associated with second trimester CO exposure.

Severity of preeclampsia is rarely studied and in our study, risk for severe preeclampsia was not increased by air pollution. Two prior reports (Dadvand et al., 2013; Malmqvist et al., 2013) have attempted to look at classifications of preeclampsia, either mild/severe or early/late onset. Dadvand and colleagues (Dadvand et al., 2013) used spatio-temporal models of PM, NO_2 and NO_x in Barcelona, Spain and found overall preeclampsia risk was increased 51% preeclampsia risk for third trimester $PM_{2.5}$ and 39% increased risk for $PM_{2.5}$ absorbance (a proxy for elemental carbon) but early onset preeclampsia was not associated with air pollutants. We observed no effect of $PM_{2.5}$ in our data, but we observed an effect for elemental carbon in the second trimester for non-asthmatics, and a significant interaction with maternal asthma and 11% increased risk for whole pregnancy exposure. We also observed a significant interaction between maternal asthma and NO_x in the first trimester that suggests increased risk for preeclampsia among asthmatics. Somewhat similar findings were seen in southern Sweden where traffic data was used to model NOx exposure and significant effects were observed for both mild and severe preeclampsia across all trimesters although the effects were more consistent for mild cases (Malmqvist et al., 2013). Also with regard to traffic, the Barcelona group examined sources and found that brake dust and total traffic exposure associated with PM_{10} appeared to increase preeclampsia risk (Dadvand et al., 2014) but no associations with proximity to roadways was observed in Rotterdam (van den Hooven et al., 2009).

Beyond elemental carbon, which was estimated in Barcelona (Dadvand et al., 2013), the other constituents of $PM_{2.5}$ have not been studied in relation to preeclampsia. We observed increased risks in the second trimester for organic compounds and for dust particles as well as elemental carbon. Whole pregnancy average dust was also associated with preeclampsia. Significant interaction with asthma was only observed for whole pregnancy elemental carbon exposure, with higher risks among asthmatics but the overall patterns of risk do not suggest differential effects by asthma status.

Our novel results for VOC and PAH exposures were striking and we hope that they stimulate further research in this area. Nearly all of the VOCs studied demonstrated a differential effect with significantly higher risk among asthmatics than in the non-asthmatic group. Risks were generally higher later in pregnancy or with whole pregnancy averages. The interaction models revealed increased risks for asthmatic mothers for many compounds at all time points studied suggesting a more persistent vulnerability for women with asthma. With regard to PAH exposure, increased risks were less common and tended to be of smaller magnitude than those observed for VOCs. Second trimester and/or whole pregnancy average exposures were associated with preeclampsia for acenaphthene, acenaphthylene, fluoranthene, fluorene, and pyrene. Interaction with maternal asthma was also less common for ambient PAH exposure, with the exception of naphthalene and fluoranthene. These findings merit further attention both in ambient exposure studies as well as in occupational settings.

The literature is exceedingly sparse for VOC exposure and either preeclampsia or hypertension. VOC exposure is most commonly related to new carpets, adhesives, upholstery, manufactured wood or leather goods, and in some pesticides or cleaning fluids. Cigarette smoke is also a major source of benzene exposure. Exposure to benzene has been associated impaired pregnancy maintenance in both human and animal studies (Cummings and Kavlock, 2004). On the other hand, tap water exposure to benzene did not increase hypertension in a US population (Burg and Gist, 1998). A worker exposed to high levels of methyl ethyl ketone and toluene from adhesive vapor became ill with symptoms that included elevated blood pressure (Mills et al., 2012). High levels of toluene appear to raise blood pressure (Chang et al., 2010; Capron and Logan, 2009), but lower levels may not (Chang et al., 2010). We have also previously found that acute exposure to several VOCs and some PAHs elevate blood pressure among women with new onset hypertensive disorders of pregnancy (Mannisto et al., 2014). Our findings at very low ambient exposure levels among pregnant women, particularly those with asthma, merit further attention both in ambient exposure studies as well as in occupational settings.

Our study is limited by the use of the hospital referral region as the geographic unit for our exposure time-windows. Women may move during pregnancy, so the earlier time windows in particular may suffer from misclassification of exposure. On the other hand, averaging over the hospital referral region will capture some local mobility as well as indicate average exposure for most of the cohort who are likely to live within the referral region of their delivery hospital. In addition, because air pollution is regulated at the population level, studies identifying regional-level air pollution levels that are associated with increased risk for preeclampsia will be informative for regulatory and public health agencies. We also adjust all of our analyses for study site as a way to control for potential differences in medical record recording and other unmeasured factors, but site also explains some of the variance in air pollutants, making our estimates somewhat conservative. For some time windows, we observed inverse associations between pollutants and preeclampsia. We do not anticipate increases in air pollution exposure to biologically confer protection but they may be chance findings or related to the negative correlations among pollutants. We did not adjust our findings for multiple comparisons because of the exploratory nature of the analyses (Rothman, 1990) but the number of significant interactions with maternal asthma suggests a pattern of findings above chance. Finally, we recognize that although the intrapartum electronic medical records provide rich clinical data, we did not have access to the specific week in gestation when preeclampsia was diagnosed, asthma severity or treatment which could have impacted our findings. As such, we used the severe preeclampsia diagnosis as a marker of early onset and note that a diagnosis will often trigger a medically indicated delivery within a relatively short time frame. We also assume our findings represent the experience of the average asthma patient and those with more severe disease could have a more complicated course.

The strengths of our study include detailed exposure models which account for weather and have both temporal and spatial dispersion with multiple sites across the US over an 8-year period. The large, contemporary, obstetric database allows us to control for detailed clinical data that are not available or unreliably reported in administrative sources such as birth certificates or insurance data.

5. Conclusions

This is the first study to comprehensively study the interaction of maternal asthma, a common chronic disease in contemporary obstetric practice known to increase preeclampsia risk, and air pollutant exposures. We find many exposures that differentially increase preeclampsia risk for women with asthma, suggesting they are a particularly vulnerable population.

Consistent with a recent meta-analysis of preeclampsia, we found no effect for most criteria air pollutants on preeclampsia risk with the exception of a 10% increased risk among asthmatics associated with second trimester CO exposure. We also observed few interactions with maternal asthma for the commonly measured criteria air pollutants with the exception of first trimester NO_x and SO_2. In contrast, we see a strong signal for most VOC exposures, particularly for women with asthma. These results merit further investigation and suggest that women with asthma, who already experience higher rates of preeclampsia, may be a vulnerable subpopulation with respect to air pollution exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

$PM_{2.5}$	Particulate Matter < 2.5 μm
NO_2	nitrogen dioxide
NOx	nitrogen oxides
PM_{10}	Particulate Matter < 10 μm
CO	carbon monoxide
O_3	ozone

PAHs	polycyclic aromatic hydrocarbons
VOCs	volatile organic compounds
ICD-9	International Classification of Diseases, Ninth Revision
CMAQ	Community Multiscale Air Quality
IQR	interquartile range
BMI	body mass index

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Table 1

Descriptive statistics by preeclampsia and asthma status, Consortium on Safe Labor/Air Quality and Reproductive Health Study, 2002–2008 (N = 210,508).

		Normotensive		Preeclampsia	
		n = 199,980		n = 10,528	
		Asthma n = 14,789	No asthma n = 185,191	Asthma n = 918	No asthma n = 9610
Age, mean (SD)		26.1 (6.1)	27.6 (6.1)	26.2 (6.8)	27.2 (6.6)
Race, n (%)	White	7192 (6.8)	93,349 (88.8)	423 (0.4)	4176 (4.0)
	Black	4556 (10.0)	37,963 (83.2)	314 (0.7)	2799 (6.1)
	Hispanic	2028 (5.5)	33,159 (89.8)	115 (0.3)	1616 (4.4)
	Asian/Pacific Islander	188 (2.1)	8395 (93.7)	10 (0.1)	371 (4.1)
	Other/Unknown	825 (6.0)	12,325 (89.0)	56 (0.4)	648 (4.7)
Pre-pregnancy BMI, n (%)	Underweight	436 (5.6)	7143 (91.7)	10 (0.1)	199 (2.6)
	Normal weight	4270 (5.6)	69,689 (91.1)	179 (0.2)	2379 (3.1)
	Overweight	2301 (7.3)	27,462 (87.6)	131 (0.4)	1470 (4.7)
	Obese	2450 (10.1)	19,964 (82.0)	228 (0.9)	1699 (7.0)
	Unknown	5332 (7.6)	60,933 (86.4)	370 (0.5)	3863 (5.5)
Parity, n (%)	Nulliparous	5739 (6.9)	71,554 (85.8)	538 (0.7)	5587 (6.7)
	Primiparous	4,522 (7.0)	58,345 (89.7)	182 (0.3)	2016 (3.1)
	Multiparous	4528 (7.3)	55,292 (89.2)	198 (0.3)	2007 (3.2)
Marital status, n (%)	Married	6492 (5.2)	112,610 (90.4)	386 (0.3)	5020 (4.0)
	Not married	7591 (9.7)	66,944 (85.5)	532 (0.7)	3234 (4.1)
	Unknown	706 (10.6)	5637 (84.7)	43 (0.7)	268 (4.0)
Insurance status, n (%)	Private	7767 (6.6)	104,873 (88.5)	495 (0.4)	5365 (4.5)
	Public	6121 (9.1)	57,331 (85.5)	365 (0.5)	3234 (4.8)
	Self-pay, other, or unknown	901 (3.6)	22,987 (92.1)	58 (0.2)	1011 (4.1)
Smoking during pregnancy, n (%)		1813 (13.0)	11,551 (82.8)	89 (0.6)	502 (3.6)
Alcohol use during pregnancy, n (%)		463 (12.2)	3171 (83.3)	25 (0.7)	148 (3.9)

Table 2

Adjusted[a] risk ratios (and 95% confidence intervals) for preeclampsia per IQR unit increase[b] in pollutant by exposure window and asthma status, Consortium on Safe Labor/Air Quality and Reproductive Health Study, 2002–2008 (N = 210,508).

		Preconception	First trimester	Second trimester	Whole pregnancy
		RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
CO	Asthma	1.03 (0.94–1.13)	1.03 (0.93–1.13)	1.10 (1.00–1.20)	1.08 (0.99–1.18)
	No asthma	0.99 (0.95–1.03)	0.96 (0.93–1.00)	1.01 (0.97–1.04)	1.01 (0.96–1.05)
NO_X	Asthma	1.05 (0.94–1.16)	**1.05 (0.95–1.17)**[c]	1.07 (0.96–1.20)	1.06 (0.94–1.20)
	No asthma	0.98 (0.94–1.03)	**0.94 (0.90–0.98)**	0.98 (0.94–1.03)	0.97 (0.89–1.04)
O_3	Asthma	1.03 (0.93–1.14)	0.99 (0.89–1.09)	1.00 (0.90–1.10)	0.98 (0.88–1.09)
	No asthma	1.01 (0.97–1.05)	1.03 (0.99–1.06)	0.96 (0.93–1.00)	0.95 (0.91–1.01)
SO_2	Asthma	1.04 (0.96–1.13)	**1.02 (0.94–1.11)**[c]	1.05 (0.98–1.13)	1.06 (0.96–1.17)
	No asthma	0.98 (0.94–1.01)	**0.93 (0.90–0.97)**	1.00 (0.97–1.03)	0.98 (0.92–1.05)
PM_{10}	Asthma	0.91 (0.83–1.00)	1.02 (0.94–1.12)	0.99 (0.90–1.08)	1.01 (0.93–1.10)
	No asthma	0.98 (0.95–1.02)	1.03 (0.99–1.06)	1.02 (0.99–1.06)	1.04 (0.99–1.08)
$PM_{2.5}$	Asthma	0.95 (0.85–1.07)	1.03 (0.93–1.16)	1.01 (0.91–1.13)	1.07 (0.93–1.24)
	No asthma	0.97 (0.93–1.02)	0.99 (0.94–1.04)	0.99 (0.95–1.04)	1.02 (0.94–1.11)
$PM_{2.5}$ constituents					
Elemental carbon	Asthma	1.06 (0.97–1.16)	1.06 (0.95–1.18)	1.10 (0.99–1.22)	**1.11 (1.03–1.21)**[c]
	No asthma	1.02 (0.98–1.06)	0.98 (0.93–1.03)	1.05 (1.00–1.10)	**1.03 (0.99–1.06)**
Ammonium particles	Asthma	0.99 (0.89–1.11)	1.03 (0.88–1.21)	1.01 (0.87–1.19)	1.06 (0.93–1.20)
	No asthma	1.02 (0.98–1.07)	0.96 (0.88–1.05)	1.03 (0.93–1.13)	1.03 (0.96–1.09)
Nitrate particles	Asthma	1.03 (0.93–1.14)	1.06 (0.96–1.17)	1.05 (0.95–1.15)	1.05 (0.95–1.17)
	No asthma	1.02 (0.98–1.05)	0.96 (0.93–0.99)	1.02 (0.98–1.05)	0.99 (0.95–1.05)
Organic compounds	Asthma	1.05 (0.96–1.15)	1.05 (0.93–1.19)	1.08 (0.95–1.22)	1.09 (0.98–1.21)
	No asthma	1.02 (0.98–1.06)	0.96 (0.91–1.02)	1.09 (1.03–1.16)	1.02 (0.96–1.08)
Sulfite particles	Asthma	0.95 (0.87–1.04)	1.05 (0.93–1.18)	0.92 (0.82–1.03)	0.99 (0.87–1.12)
	No asthma	0.99 (0.96–1.03)	1.07 (1.00–1.15)	0.95 (0.88–1.01)	1.01 (0.93–1.09)
Dust particles	Asthma	0.99 (0.92–1.06)	1.03 (0.95–1.10)	1.03 (0.96–1.10)	1.04 (0.97–1.12)
	No asthma	1.02 (0.98–1.06)	1.03 (0.99–1.06)	1.06 (1.02–1.10)	1.07 (1.02–1.12)

[a] Models are adjusted for maternal race/ethnicity, age, parity, pre-pregnancy BMI, smoking and alcohol use, insurance status, marital status and study site. The estimates are based on the interaction of maternal asthma and each pollutant derived from a single model, not stratified analyses.

[b] Distributions and IQRs are shown in Supplemental Table 1.

[c] Estimates in bold indicate significant interaction between pollutant and maternal asthma $p < 0.05$.

Table 3

Adjusted[a] risk ratios (and 95% confidence intervals) for preeclampsia associated with high exposure[b] to volatile organic compounds by exposure window and asthma status, Consortium on Safe Labor/Air Quality and Reproductive Health Study, 2002–2008 (n = 210,508).

		Preconception	First trimester	Second trimester	Whole pregnancy
		RR (95% CI)	**RR (95%CI)**	**RR (95% CI)**	**RR (95% CI)**
Benzene	Asthma	**1.16 (0.98–1.38)**[c]	**1.13 (0.95–1.34)**[c]	**1.39 (1.16–1.65)**[c]	**1.43 (1.11–1.83)**[c]
	No asthma	**0.98 (0.89–1.07)**	**0.87 (0.80–0.95)**	**1.15 (1.04–1.27)**	**1.18 (0.97–1.44)**
1,3-Butadiene	Asthma	0.99 (0.85–1.16)	**1.06 (0.91–1.23)**[c]	1.02 (0.87–1.19)	0.98 (0.84–1.15)
	No asthma	1.02 (0.96–1.08)	**1.02 (0.96–1.09)**	1.03 (0.96–1.11)	1.03 (0.96–1.10)
Ethylbenzene	Asthma	**1.30 (1.07–1.58)**[c]	**1.23 (1.02–1.49)**[c]	**1.26 (1.04–1.53)**[c]	**1.70 (1.42–2.04)**[c]
	No asthma	**1.09 (0.95–1.26)**	**0.99 (0.87–1.13)**	**1.06 (0.93–1.22)**	**1.42 (1.26–1.61)**
Cyclohexane	Asthma	**1.13 (0.96–1.32)**[c]	**1.19 (1.02–1.39)**[c]	1.14 (0.98–1.33)	**1.31 (1.11–1.54)**[c]
	No asthma	**0.89 (0.83–0.97)**	**0.99 (0.92–1.06)**	0.99 (0.92–1.06)	**1.08 (1.00–1.18)**
Methyl-tertiary butyl ether	Asthma	1.04 (0.89–1.21)	1.09 (0.94–1.27)	1.14 (0.98–1.33)	1.11 (0.96–1.30)
	No asthma	1.01 (0.96–1.06)	1.00 (0.95–1.05)	1.00 (0.94–1.05)	0.99 (0.94–1.05)
N-hexane	Asthma	1.17 (0.99–1.38)	**1.16 (0.98–1.36)**[c]	**1.28 (1.08–1.51)**[c]	**1.54 (1.20–1.97)**[c]
	No asthma	1.03 (0.95–1.12)	**0.95 (0.88–1.03)**	**1.05 (0.96–1.14)**	**1.28 (1.05–1.55)**
Methyl ethyl ketone	Asthma	1.02 (0.87–1.18)	**1.24 (1.07–1.44)**[c]	**1.24 (1.06–1.44)**[c]	**1.23 (1.05–1.44)**[c]
	No asthma	0.96 (0.91–1.01)	**0.97 (0.92–1.03)**	**0.97 (0.92–1.03)**	**0.98 (0.91–1.05)**
M-xylene	Asthma	**1.22 (1.00–1.50)**[c]	**1.23 (1.01–1.51)**[c]	**1.34 (1.11–1.62)**[c]	**1.56 (1.29–1.87)**[c]
	No asthma	**1.01 (0.87–1.17)**	**1.00 (0.87–1.16)**	**1.11 (0.97–1.27)**	**1.25 (1.11–1.41)**
O-xylene	Asthma	**1.16 (0.95–1.41)**[c]	**1.18 (0.96–1.43)**[c]	**1.41 (1.17–1.70)**[c]	**1.38 (1.14–1.68)**[c]
	No asthma	**0.91 (0.79–1.05)**	**0.94 (0.82–1.08)**	**1.19 (1.04–1.35)**	**1.11 (0.96–1.28)**
P-xylene	Asthma	**1.28 (1.08–1.52)**[c]	**1.20 (1.00–1.44)**[c]	**1.22 (1.02–1.47)**[c]	**1.62 (1.35–1.95)**[c]
	No asthma	**1.09 (0.98–1.21)**	**0.97 (0.86–1.10)**	**1.02 (0.90–1.16)**	**1.33 (1.17–1.49)**
Propene	Asthma	0.93 (0.80–1.08)	**1.15 (1.00–1.33)**[c]	1.08 (0.93–1.24)	**1.17 (1.01–1.36)**[c]
	No asthma	0.99 (0.95–1.04)	**0.98 (0.94–1.03)**	0.99 (0.94–1.04)	**0.99 (0.93–1.04)**
Sesquiterpene	Asthma	1.12 (0.97–1.30)	1.16 (1.00–1.35)	1.02 (0.88–1.19)	1.06 (0.90–1.23)
	No asthma	1.05 (0.99–1.11)	1.01 (0.96–1.07)	1.06 (1.00–1.12)	0.99 (0.92–1.06)

		Preconception	First trimester	Second trimester	Whole pregnancy
		RR (95% CI)	**RR (95%CI)**	**RR (95% CI)**	**RR (95% CI)**
Styrene	Asthma	0.96 (0.83–1.11)	1.04 (0.89–1.21)	0.97 (0.82–1.13)	0.95 (0.81–1.12)
	No asthma	1.02 (0.97–1.09)	1.06 (0.99–1.12)	1.03 (0.97–1.11)	1.01 (0.94–1.08)
Toluene	Asthma	**1.17 (0.97–1.41)**[c]	**1.31 (1.08–1.59)**[c]	**1.38 (1.15–1.66)**[c]	**1.36 (1.12–1.66)**[c]
	No asthma	**0.91 (0.80–1.04)**	**1.07 (0.93–1.22)**	**1.14 (1.00–1.30)**	**1.10 (0.96–1.26)**

[a]Models are adjusted for maternal race/ethnicity, age, parity, pre-pregnancy BMI, smoking and alcohol use, insurance status, marital status and study site. The estimates are based on the interaction of maternal asthma and each pollutant derived from a single model, not stratified analyses.

[b]Distributions are shown in Supplemental Table 1. Pollutant levels were dichotomized at the 75th percentile and high exposure is that upper quartile compared to the rest of the distribution.

[c]Estimates in bold indicate significant interaction between pollutant and maternal asthma $p < 0.05$.

Table 4

Adjusted[a] risk ratios (and 95% confidence intervals) for preeclampsia associated with high exposure[b] to polycyclic aromatic hydrocarbons by exposure window and asthma status, Consortium on Safe Labor/Air Quality and Reproductive Health Study, 2002–2008 (N = 210,508).

		Preconception	First trimester	Second trimester	Whole pregnancy
		RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Acenaphthene	Asthma	1.05 (0.91–1.20)	1.10 (0.96–1.26)	1.08 (0.94–1.25)	1.03 (0.89–1.18)
	No asthma	1.00 (0.95–1.05)	0.97 (0.92–1.02)	1.06 (1.01–1.11)	1.07 (1.01–1.13)
Acenaphthylene	Asthma	1.04 (0.91–1.19)	1.13 (0.99–1.29)	1.05 (0.92–1.20)	1.03 (0.90–1.19)
	No asthma	0.99 (0.93–1.04)	0.99 (0.93–1.04)	1.05 (0.99–1.10)	1.09 (1.03–1.16)
Anthracene	Asthma	0.95 (0.83–1.08)	1.04 (0.91–1.18)	1.00 (0.87–1.14)	1.09 (0.95–1.25)
	No asthma	1.05 (1.00–1.10)	1.02 (0.97–1.07)	0.98 (0.94–1.03)	1.04 (0.98–1.10)
Benzo[*a*]-anthracene	Asthma	0.90 (0.78–1.05)	1.12 (0.97–1.29)	1.07 (0.93–1.24)	1.09 (0.94–1.26)
	No asthma	1.02 (0.97–1.07)	0.98 (0.94–1.03)	0.95 (0.90–1.00)	0.99 (0.94–1.04)
Benzo[*a*]-pyrene	Asthma	1.07 (0.93–1.22)	1.01 (0.88–1.15)	0.95 (0.83–1.09)	1.03 (0.90–1.18)
	No asthma	0.97 (0.92–1.02)	0.96 (0.92–1.01)	0.99 (0.94–1.03)	1.04 (0.99–1.09)
Chrysene	Asthma	1.04 (0.91–1.18)	1.07 (0.93–1.22)	1.03 (0.90–1.19)	0.99 (0.87–1.13)
	No asthma	0.95 (0.91–1.00)	0.96 (0.92–1.01)	1.01 (0.96–1.07)	0.99 (0.94–1.04)
Fluoranthene	Asthma	**1.15 (1.01–1.32)**[c]	1.07 (0.93–1.23)	1.07 (0.93–1.23)	1.11 (0.96–1.27)
	No asthma	**1.00 (0.95–1.05)**	0.97 (0.92–1.03)	1.08 (1.03–1.14)	1.02 (0.96–1.07)
Fluorene	Asthma	1.05 (0.92–1.20)	1.09 (0.95–1.25)	1.08 (0.94–1.24)	1.06 (0.93–1.22)
	No asthma	1.01 (0.96–1.06)	0.97 (0.92–1.02)	1.07 (1.02–1.12)	1.08 (1.02–1.14)
Ideno[1,2,3-Cd]pyrene	Asthma	1.07 (0.93–1.22)	1.01 (0.88–1.16)	0.94 (0.82–1.08)	1.02 (0.89–1.17)
	No asthma	0.96 (0.92–1.01)	0.97 (0.92–1.01)	0.97 (0.93–1.02)	0.98 (0.93–1.03)
Naphthalene	Asthma	**1.12 (0.96–1.29)**[c]	1.04 (0.90–1.20)	**1.21 (1.05–1.40)**[c]	**1.21 (1.04–1.42)**[c]
	No asthma	**0.91 (0.84–0.99)**	0.90 (0.83–0.98)	**1.04 (0.96–1.11)**	**0.96 (0.88–1.06)**
Phenanthrene	Asthma	1.07 (0.94–1.22)	1.03 (0.90–1.18)	1.02 (0.89–1.17)	1.06 (0.93–1.21)
	No asthma	1.00 (0.95–1.05)	0.95 (0.91–1.00)	1.04 (0.99–1.09)	0.99 (0.95–1.04)
Pyrene	Asthma	1.12 (0.97–1.29)	1.06 (0.91–1.22)	1.05 (0.91–1.22)	1.15 (0.99–1.33)
	No asthma	0.99 (0.94–1.04)	0.97 (0.92–1.03)	1.04 (0.99–1.10)	1.07 (1.00–1.14)

[a]Models are adjusted for maternal race/ethnicity, age, parity, pre-pregnancy BMI, smoking and alcohol use, insurance status, marital status and study site. The estimates are based on the interaction of maternal asthma and each pollutant derived from a single model, not stratified analyses.

[b] Distributions are shown in Supplemental Table 1. Pollutant levels were dichotomized at the 75th percentile and high exposure is that upper quartile compared to the rest of the distribution.

[c] Estimates in bold indicate significant interaction between pollutant and maternal asthma $p < 0.05$.