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Original Contribution

Ambient Air Pollution and Risk of Gestational Hypertension

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Air pollution has been linked to hypertension in the general population, but data on gestational hypertension (GH) are limited. We investigated criteria air pollutants and air toxics during the period before conception and in early gestation in relation to GH risk in the Consortium on Safe Labor/Air Quality and Reproductive Health Study (United States, 2002–2008). Modified Community Multi-scale Air Quality models estimated air pollution exposures for 6,074 singleton pregnancies in which GH was present and 199,980 normotensive pregnancies. Generalized estimating equations estimated relative risks per interquartile-range increment for pollutants and high exposure (≥75th percentile) for air toxics after adjustment for major risk factors. For an interquartile-range increment, GH risk was significantly increased by 18% for sulfur dioxide during the 3 months before conception and, during gestational weeks 1–20, 17% for nitrogen oxides, 10% for particulate matter with an aerodynamic diameter <2.5 μm, 7% for particulate matter with an aerodynamic diameter <10 μm, and 22% for sulfur dioxide. High exposures to several polycyclic aromatic hydrocarbons before conception and during the first trimester were significantly associated with 8%–20% higher risk of GH. Further, preconceptional exposures to several volatile organic compounds were significantly associated with 11%–19% higher risk. Our findings suggest that early exposures to criteria air pollutants, particularly from transport emissions, and high exposure to several air toxics before conception may increase GH risk.

ambient air pollution; gestational hypertension; polycyclic aromatic hydrocarbons; volatile organic compounds

Abbreviations: CI, confidence interval; CMAQ, Community Multi-scale Air Quality; CSL, Consortium on Safe Labor; GH, gestational hypertension; IQR, interquartile range; NO_x, nitrogen oxides; PAH, polycyclic aromatic hydrocarbon; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter less than or equal to 10 μm; SO_2, sulfur dioxide; VOC, volatile organic compound.

Hypertensive disorders are the second leading cause of maternal mortality, accounting for 14% of such deaths worldwide between 2003 and 2009 (1). Emerging data have linked air pollution to hypertensive disorders (2). In particular, pregnancy is characterized by profound hemodynamic changes in response to the needs of the developing fetus (3). Air pollution may induce systematic oxidative stress, vascular inflammation, and endothelial dysfunction (4, 5), which can potentially elevate blood pressure. Therefore, periconceptional exposure to air pollution may aggravate physiologic changes in the vascular system and predispose women to hypertensive complications during pregnancy (6).

As a leading cause of maternal morbidity and mortality (7) and a significant risk factor for future cardiovascular disease (8), hypertensive disorders during pregnancy comprise a wide spectrum of severity and phenotypes (9). Indeed, 2 recent meta-analyses suggest heterogeneity in the association between air pollution and various pregnancy hypertensive disorders (10, 11), among which gestational hypertension (GH) is common but has received less research attention. Specifically, given that only 3 (12–14) of 17 studies in one meta-analysis (10) reported specific data on GH, no synthesis could be derived for this outcome separately. Furthermore, several important methodological issues preclude firm conclusions from the previous data.

First, 16 of the 17 studies included in the meta-analysis by Pedersen et al. (10) used birth certificate data, which often do not allow separation of GH from other subtypes of hypertensive disorders during pregnancy, as opposed to medical records and/or hospital discharge data. Second, all 3 studies on air pollution and GH as a separate outcome are single-city based (12–14), if not from a single hospital (12), which potentially limits exposure contrasts (15). In the few studies with a relatively large geographic coverage, none adjusted for location or used any other approaches to reduce residual confounding due to spatial factors (10). Further, data on more source-specific measures are lacking, such as elemental composition of the particulate matter and hazardous air toxics, including polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs). Finally, given the potential for lag effects of air pollution (16), evaluation of the previously unexamined chronic preconceptional exposure is warranted.

In view of the inconsistencies of previous findings and to further address the remaining critical data gaps, we aimed to investigate the associations of maternal exposure to criteria air pollutants (carbon monoxide, nitrogen oxides (NO_x), ozone, particulate matter with aerodynamic diameter <2.5 and <10 μm ($PM_{2.5}$ and PM_{10}), and sulfur dioxide (SO_2)), $PM_{2.5}$ constituents (elemental carbon, ammonium particles, nitrate particles, organic compounds, sulfite particles, dust particles), and air toxics (PAHs and VOCs) during preconception and early gestation with risk of GH, in a contemporary nationwide US cohort.

METHODS

Study population

The Consortium on Safe Labor (CSL) was a retrospective, nationwide cohort study of labor and delivery that included 12 clinical centers (19 hospitals, 15 nonoverlapping hospital referral regions) across the United States. As previously described in detail (17), data on maternal demographic characteristics, medical history, labor, delivery, and obstetric and neonatal outcomes of 228,438 births at ≥23 weeks of gestation were extracted from electronic medical records from 2002–2008. We excluded pregnancies with multiple gestation ($n = 5,053$) and missing air quality data ($n = 10$) or maternal age ($n = 307$) as well as those in which the women had chronic hypertension ($n = 4,358$) or superimposed preeclampsia ($n = 1,889$) and thus were not at risk for new-onset hypertension during pregnancy (9). We further excluded women with other hypertensive disorders during pregnancy (i.e., preeclampsia ($n = 10,528$) and eclampsia ($n = 239$)) to allow comparison of women with GH ($n = 6,074$) to a normotensive reference group ($n = 199,980$). This resulted in an analytical sample of 206,054 singleton pregnancies among 188,658 women, 92% of whom contributed 1 pregnancy during the study period. The study was approved by the institutional review boards of all participating institutions noted in the acknowledgements. All records were anonymized and individual patient consent was not required.

Outcome ascertainment

Women with GH, with an onset at or after week 20 of gestation by definition during the study period (2002–2008) (9), were identified from electronic medical records and/or the maternal discharge summary using *International Classification of Diseases, Ninth Revision*, diagnostic codes (642.30–642.34). Most likely, the medical record diagnoses were consistent with clinical practice of the time, although the precise date or clinical details of the diagnoses were not available. Further, although the use of electronic medical record data for ascertainment of GH in particular has not been validated, previous validation studies of the CSL data comparing systematically extracted electronic medical record data against manually abstracted chart data showed high validity (range, 91.9%–99.9%) for other perinatal outcomes, suggesting the reasonably accurate representation of electronic medical records for medical charts (17).

Exposure assessment

The Air Quality and Reproductive Health Study developed detailed air quality assessment models in 2013 for CSL patient data, and we linked the medical record data described above to exposure assessments (18). Exposures to ambient air pollutants (criteria pollutants, $PM_{2.5}$ constituents, and hazardous air toxics) were estimated using a modified version of Community Multi-scale Air Quality (CMAQ) model 4.7.1 with a 36-km horizontal resolution domain (18). Due to the anonymity of the CSL data, air pollutant exposures were based on the average pollutant concentrations in women's delivery hospital referral region (range, 415–312,644 km^2) during each of the specified exposure windows (19). The CMAQ simulations were based on the meteorology data derived from the Weather Research and Forecasting model and emission data generated using the US Environmental Protection Agency National Emissions Inventory. Model results were weighted to reflect population density within the hospital referral region, discounting areas where women were unlikely to live and work. Hourly measurements of pollutant exposures were calculated over the entire US continent from 2001–2010 in the Air Quality and Reproductive Health study as previously described (20).

Despite the wide use of the CMAQ model in estimating regional air quality, potential biases in meteorology and emission inputs, uncertainties of other model components, and issues with spatial resolution can compromise the precision in estimation (20). Thus, we used an inverse distance weighted method to recalibrate the raw CMAQ estimations for criteria pollutants using observational air-quality monitor data retrieved from the US Environmental Protection Agency Air Quality System. This observation-fused technique led to significant improvement of the model performance and was demonstrated to best account for spatial variation in air pollutants and population density as compared with 4 alternative methods (20). Constituents of $PM_{2.5}$, PAHs, and VOCs were based on raw CMAQ model output due to the lack of routinely monitored data on these pollutants. To address potentially critical timing of exposures, we assessed exposures across several a priori

time windows: 3 months before conception (as a proxy of preconceptional chronic exposure), the first trimester (gestational weeks 1–13), and a 20-week average from weeks 1–20 (as a proxy of the average gestational exposure before diagnosis). Because GH is diagnosed after 20 weeks by definition, these exposure windows were selected to precede diagnosis. Gestational age in weeks was calculated from gestational age at delivery using the best obstetrical estimate as recorded in the medical record.

Covariates

A priori selected covariates were extracted from medical records: age at childbirth (continuous), race/ethnicity (white, black, Hispanic, Asian/Pacific Islander, other/unknown), marital status (married, unmarried, missing/unknown), insurance (private, public, self-pay/other), parity (nulliparous, multiparous), prepregnancy body mass index (calculated as weight (kg)/height $(m)^2$; <18.5, 18.5–24.9, 25.0–29.9, ≥30.0, or unknown), preexisting chronic disease (any (diabetes mellitus, asthma, thyroid disease, or human immunodeficiency virus), none), smoking during pregnancy (yes, no), alcohol consumption during pregnancy (yes, no), and season of conception (spring, summer, fall, winter). Analyses were also adjusted for study site to account for both measured and unmeasured area-level indicators, including but not limited to socioeconomic status, case ascertainment, and sources of air pollution exposures. Given the small percentages of missing data on race/ethnicity (4.2%) and marital status (3.1%), missing/unknown categories were assigned for each. To reduce bias due to a relatively high proportion of missing data on prepregnancy body mass index (n = 68,322, 33%), we used multiple imputation based on all other covariates, exposures of interest, and GH status to create 10 complete datasets, and we combined the analytical results on each complete dataset using Rubin's rule (21).

Statistical analysis

Pregnancy was the unit of analysis in all statistical testing. Descriptive statistics for participant characteristics were presented as mean (standard deviation) for continuous variables and percentages for categorical variables. P values for comparing participant characteristics by status of GH were obtained from unadjusted generalized estimating equations, with robust standard errors to account for multiple pregnancies of the same woman during the study period. Distributions of exposures to criteria air pollutants and air toxics were presented as median and interquartile range (IQR) during each of the specified time windows.

Examination of the associations between criteria air pollutants in quartiles and risk of GH suggested a linear relationship. Therefore, criteria air pollutants and $PM_{2.5}$ constituents were parameterized as per IQR in their original scale for ease of interpretation and comparability to previous data (10, 11). Generalized estimating equations with a log link function (22) were fitted to estimate relative risk and 95% confidence interval for GH per IQR increment of each criteria air pollutant and $PM_{2.5}$ constituent during the specified exposure windows, adjusting for the covariates listed above. The robust sandwich standard errors were calculated to account for misspecified mean-variance relationship as well as clustering due to multiple births of the same woman during the study period. For hazardous air toxics (because PAHs and VOCs were generally observed at very low levels, and the exposures estimated by the CMAQ model were not fused with existing monitor data), we dichotomized the exposure to estimate risk associated with high exposure (≥75th percentile) rather than assuming a linear model. In addition to the fact that the CMAQ model accounts for biochemical reactions among air pollutants, effects of weather, and long-term sources of pollutants (18), multicollinearity among air pollutants derived from the same model remains a major methodological concern in multipollutant models. Therefore, criteria air pollutants and air toxics were fitted in the single-pollutant model separately during each exposure window. Post hoc multiple-comparison adjustment for P values was performed using the Benjamini-Hochberg false discovery rate–controlling method (23) within each exposure window for criteria air pollutants, $PM_{2.5}$ constituents, PAHs, and VOCs. The false discovery rate–controlling method was designed to control the expected proportion of falsely rejected hypotheses, which has greater power than methods controlling the family-wise type I error rate, such as Bonferroni correction (23).

To evaluate the robustness of the findings, we performed a series of sensitivity analyses. First, we stratified the analyses by parity and smoking, given the decrease in risk with higher parity and smoking (24). We also performed sensitivity analysis restricted to women who had complete data on prepregnancy body mass index (n = 137,732, 67%). Finally, to assess the impact of potential exposure misclassification due to the use of the hospital referral region as the geographic unit (given the anonymity of the CSL data), we performed simulation extrapolation procedures (25) on SO_2 during the first trimester as an illustration of the potential exposure misclassification, assuming an additive measurement error rate of 10% or 20% within each site. The simulation extrapolation method was performed in 3 steps implemented in R package "simex": 1) added known increments of measurement error to the data; 2) estimated the regression parameter of interest with the contaminated data; and 3) established a trend of the parameter estimates and extrapolated back to the case of no measurement error. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and R, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among 206,054 singleton deliveries, we identified 6,074 (3%) pregnancies in which GH was present. Compared with their normotensive counterparts, women with GH were slightly younger, more likely to be white or black, not married, nulliparous, and overweight or obese, as well as more likely to consume alcohol during pregnancy and to have preexisting chronic diseases (Table 1). Distributions of criteria air pollutants and air toxics by exposure window are available in Web Table 1 (available at https://academic.oup.com/aje).

Risk of GH per IQR increase in criteria air pollutant was significantly increased by 18% (95% confidence interval

Table 1. Participant Characteristics by Gestational Hypertension Status ($n = 206,054$), Consortium on Safe Labor/Air Quality and Reproductive Health Study, United States, 2002–2008

Characteristic	Normotensive ($n = 199,980$)		Gestational Hypertension ($n = 6,074$)		*P* Value[a]
	No.	%	No.	%	
Maternal age, years[b]	27.5 (6.1)		26.9 (6.2)		<0.001
Race/ethnicity					<0.001
White	100,541	50.3	3,386	55.7	
Black	42,519	21.3	1,567	25.8	
Hispanic	35,187	17.6	784	12.9	
Asian/Pacific Islander	13,251	6.6	189	3.1	
Other/unknown	8,482	4.2	148	2.4	
Marital status					<0.001
Married	119,102	59.6	3,425	56.4	
Not married	74,535	37.3	2,538	41.8	
Missing/unknown	6,343	3.2	111	1.8	
Insurance					<0.001
Private	112,640	56.3	3,460	57.0	
Public	66,059	33.0	2,298	37.8	
Self-pay/other	21,281	10.6	316	5.2	
Nulliparous	77,293	38.7	3,411	56.2	<0.001
Prepregnancy BMI[b,c]	25.0 (5.9)		28.2 (7.2)		<0.001
<18.5	7,579	3.8	117	1.9	
18.5–24.9	73,959	37.0	1,497	24.6	
25–29.9	29,763	14.9	1,064	17.5	
≥30.0	22,414	11.2	1,339	22.0	
Unknown	66,265	33.1	2,057	33.9	
Smoking during pregnancy	13,364	6.7	386	6.4	0.3
Alcohol consumption during pregnancy	3,634	1.8	140	2.3	0.006
Preexisting chronic disease					
Pregestational diabetes	2,218	1.1	124	2.0	<0.001
Asthma	14,789	7.4	557	9.2	<0.001
Thyroid disease	5,700	2.9	221	3.6	<0.001
Human immunodeficiency virus	775	0.4	15	0.2	<0.001
Season of conception					0.2
Spring (March–May)	47,140	23.6	1,493	24.6	
Summer (June–August)	51,574	25.8	1,596	26.3	
Fall (September–November)	55,297	27.7	1,546	25.5	
Winter (December–February)	45,969	23.0	1,439	23.7	

Abbreviation: BMI, body mass index.

[a] *P* values were obtained by generalized estimating equations, accounting for multiple pregnancies of the same woman during the study period.

[b] Mean values (standard deviation).

[c] BMI was calculated as weight (kg)/height $(m)^2$.

(CI): 8, 29) for exposure to SO_2 during the 3 months before conception and, during the first trimester, 11% (95% CI: 1, 21) for NO_x, 8% (95% CI: 2, 15) for $PM_{2.5}$, and 22% (95% CI: 11, 34) for SO_2, after adjustment for covariates (all false discovery rate–adjusted *P* values were <0.05) (Figure 1; see Web Table 2 for point estimates). Results for criteria pollutants during gestational weeks 1–20, as a proxy of the average gestational exposure before diagnosis, were similar to those for trimester 1 (weeks 1–13). Among the constituents of $PM_{2.5}$, an IQR increment in dust particles was significantly

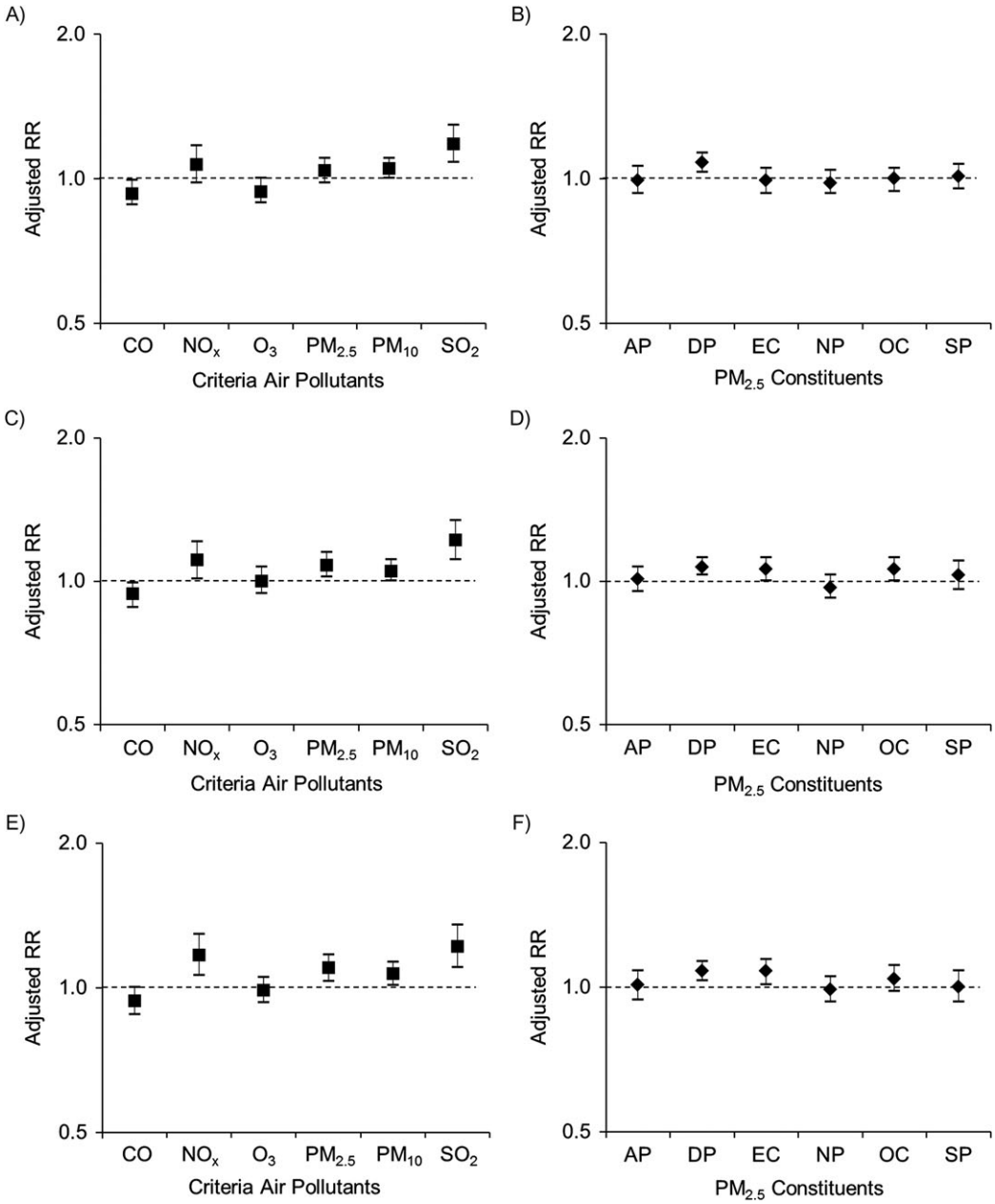

Figure 1. Adjusted relative risks (RRs) for gestational hypertension associated with an interquartile-range increment of exposure to criteria air pollutants and constituents of particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) during 3 months before conception (A, B), gestational weeks 1–13 (C, D), and gestational weeks 1–20 (E, F), Consortium on Safe Labor/Air Quality and Reproductive Health Study, United States, 2002–2008. The models adjusted for study site, maternal age, race/ethnicity, marital status, insurance, parity, prepregnancy body mass index, preexisting chronic disease, smoking during pregnancy, alcohol consumption during pregnancy, and season of conception. AP, ammonium particles; CO, carbon monoxide; DP, dust particles; EC, elemental carbon; NO_x, nitrogen oxides; NP, nitrate particles; O_3, ozone; OC, organic compounds; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; SO_2, sulfur dioxide; SP, sulfite particles. Bars, 95% confidence intervals.

associated with a 7%–8% higher risk of GH consistently across all exposure windows (Figure 1; all false discovery rate–adjusted *P* values were <0.05, Web Table 2). Moreover, an IQR increment in elemental carbon exposure across gestational weeks 1–20 was significantly associated with an 8% higher risk of GH.

After post hoc false discovery rate adjustment, higher exposures (≥75th percentile) to several PAH exposures during the 3 months before conception were positively associated with risk of GH, with a higher risk of 11% for benzo[a]-pyrene (95% CI: 3, 18), fluoranthene (95% CI: 3, 21), and ideno[1,2,3-Cd]pyrene (95% CI: 4, 19) and 20% (95% CI: 9, 32)

Table 2. Adjusted Relative Risks for Gestational Hypertension Associated With High Exposure to Polycyclic Aromatic Hydrocarbons According to Exposure Window ($n = 206,054$)[a], Consortium on Safe Labor/Air Quality and Reproductive Health Study, United States, 2002–2008

Polycyclic Aromatic Hydrocarbon	3 Months Before Conception			Trimester 1[b]			Gestational Weeks 1–20		
	RR	95% CI	*P* Value[c]	RR	95% CI	*P* Value[c]	RR	95% CI	*P* Value[c]
Acenaphthene	1.05	0.97, 1.14	0.390	1.02	0.94, 1.12	0.883	0.96	0.88, 1.05	0.783
Acenaphthylene	1.01	0.93, 1.10	0.811	1.00	0.92, 1.10	0.933	0.99	0.91, 1.08	0.832
Anthracene	0.98	0.91, 1.05	0.710	1.02	0.94, 1.10	0.883	1.02	0.95, 1.10	0.783
Benzo[a]anthracene	0.99	0.92, 1.06	0.815	1.05	0.97, 1.13	0.600	1.04	0.96, 1.12	0.783
Benzo[a]pyrene	1.11	1.03, 1.18	0.012	1.08	1.02, 1.16	0.048	1.09	1.02, 1.16	0.102
Chrysene	1.06	0.99, 1.14	0.183	1.00	0.93, 1.07	0.933	0.99	0.92, 1.06	0.783
Fluoranthene	1.11	1.03, 1.21	0.030	1.05	0.96, 1.14	0.679	1.03	0.94, 1.12	0.783
Fluorene	1.04	0.96, 1.12	0.460	1.02	0.94, 1.11	0.883	1.02	0.94, 1.11	0.783
Ideno[1,2,3-Cd]pyrene	1.11	1.04, 1.19	0.012	1.09	1.03, 1.16	0.048	1.08	1.01, 1.15	0.102
Naphthalene	1.20	1.09, 1.32	0.001	1.13	1.03, 1.25	0.048	1.07	0.96, 1.19	0.783
Phenanthrene	1.07	1.00, 1.15	0.120	0.98	0.91, 1.05	0.882	0.98	0.91, 1.05	0.783
Pyrene	1.10	1.01, 1.20	0.072	1.01	0.92, 1.11	0.932	1.04	0.94, 1.15	0.783

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for study site, maternal age, race/ethnicity, marital status, insurance, parity, prepregnancy body mass index, preexisting chronic disease, smoking during pregnancy, alcohol consumption during pregnancy, and season of conception. Levels of air toxics were dichotomized at the 75th percentile, and high exposure (≥75th percentile) was compared with the rest of the distribution.

[b] Trimester 1 refers to gestational weeks 1–13.

[c] *P* values were false discovery rate–adjusted within each exposure window.

for naphthalene (Table 2). A higher risk of GH, ranging from 8%–13%, was also observed in association with exposures ≥75th percentile to benzo[a]pyrene, ideno[1,2,3-cd]pyrene, and naphthalene during the first trimester, with slightly smaller point estimates compared with the period before conception. As for VOCs, a higher risk of GH was observed for higher exposures to cyclohexane, ethylbenzene, m-xylene, n-hexane, o-xylene, sesquiterpene, and toluene during the 3 months before conception (all false discovery rate–adjusted *P* values were <0.05, Table 3). The positive associations with o-xylene and toluene from weeks 1–20 did not persist after false discovery rate adjustment.

We observed similar results in the sensitivity analysis restricted to multiparous women ($n = 125,350$, 61%), whereas models restricted to nulliparous women did not converge due to the smaller sample size (data not shown). Likewise, results were robust among nonsmokers during pregnancy ($n = 192,304$, 93%). Findings were also similar when we restricted our analysis to women whose prepregnancy body mass index was not missing (data not shown). When we examined the potential impact of 10% or 20% exposure misclassification using simulation extrapolation procedures, we found similar results for SO_2 exposure during the first trimester in association with risk of GH (Table 4 and Web Figure 1).

DISCUSSION

In this large retrospective cohort, we observed that exposures to NO_x, $PM_{2.5}$, and SO_2 during the first trimester, and NO_x, $PM_{2.5}$, PM_{10}, and SO_2 during gestational weeks 1–20 were associated with higher risk of GH. Among $PM_{2.5}$ constituents, an IQR increment of exposure to dust particles was associated with a 7%–8% higher risk of GH during both the 3 months before conception and weeks 1–20 of gestation. Elemental carbon was only positively and significantly related to the risk during the gestational window from weeks 1–20. PAHs, benzo[a]pyrene and ideno[1,2,3-cd]pyrene, were associated with an 8%–11% higher risk across all time periods. Further, higher exposures (≥75th percentile) to several VOCs were associated with an 11%–19% higher risk only during the 3 months before conception, suggesting a potential chronic pathway as opposed to an acute one during early gestation.

Given the heterogeneity in severity and phenotype of hypertensive disorders during pregnancy (9) and inconsistent findings on these disorders as a combined outcome (10, 11), investigation of the association of air pollution with GH as a separate outcome is warranted (10, 26). Indeed, similar to findings by Savitz et al. (26), we previously demonstrated overall null associations between exposures to air pollutants during early gestation and risk of preeclampsia among nonasthmatic women (27) as opposed to findings on GH in the current study. However, among the 17 studies included in a recent meta-analysis on air pollution in relation to pregnancy-induced hypertensive disorders (10), only 3 treated GH separately (12–14). Specifically, van den Hooven et al. (13) reported a 72% increased risk of GH (95% CI: 1.12, 2.63) for whole-gestation PM_{10} exposure (per 10-$\mu g/m^3$ increase) in Rotterdam, Netherlands, whereas Lee et al. (12) observed an 11% increased risk (95% CI: 1.00, 1.23) for first-trimester $PM_{2.5}$ exposure (per IQR increase) but not for PM_{10} in Pittsburgh, Pennsylvania. These findings are generally in line with ours, although the point estimate reported in

Table 3. Adjusted Relative Risks for Gestational Hypertension Associated With High Exposure to Volatile Organic Compounds According to Exposure Window ($n = 206,054$)[a], Consortium on Safe Labor/Air Quality and Reproductive Health Study, United States, 2002–2008

Volatile Organic Compound	3 Months Before Conception			Trimester 1[b]			Gestational Weeks 1–20		
	RR	95% CI	*P* Value[c]	RR	95% CI	*P* Value[c]	RR	95% CI	*P* Value[c]
Benzene	1.06	0.94, 1.20	0.452	1.07	0.95, 1.21	0.596	1.08	0.95, 1.23	0.514
1,3-butadiene	0.98	0.91, 1.06	0.813	0.99	0.91, 1.07	0.878	1.03	0.94, 1.12	0.746
Cyclohexane	1.12	1.02, 1.23	0.042	0.99	0.90, 1.09	0.878	1.00	0.90, 1.10	0.945
Ethylbenzene	1.18	1.03, 1.35	0.042	1.09	0.94, 1.25	0.596	1.07	0.93, 1.24	0.625
Methyl-tertiary butyl ether	1.06	0.98, 1.13	0.218	1.03	0.96, 1.11	0.691	1.06	0.99, 1.15	0.228
Methyl ethyl ketone	0.99	0.91, 1.08	0.912	0.98	0.90, 1.08	0.878	0.96	0.88, 1.06	0.627
M-xylene	1.19	1.04, 1.36	0.042	1.03	0.89, 1.20	0.878	1.09	0.94, 1.27	0.514
N-hexane	1.16	1.05, 1.29	0.028	1.06	0.95, 1.18	0.596	1.03	0.92, 1.17	0.746
O-xylene	1.19	1.04, 1.36	0.042	1.23	1.07, 1.41	0.056	1.17	1.01, 1.35	0.201
P-xylene	1.13	1.00, 1.26	0.081	1.01	0.88, 1.16	0.894	1.02	0.88, 1.19	0.889
Propene	1.01	0.94, 1.08	0.912	1.02	0.95, 1.10	0.828	1.00	0.92, 1.07	0.945
Sesquiterpene	1.11	1.04, 1.20	0.028	1.07	0.99, 1.15	0.397	1.08	1.00, 1.16	0.201
Styrene	1.00	0.93, 1.08	0.912	1.07	0.98, 1.15	0.413	1.07	0.99, 1.16	0.288
Toluene	1.17	1.03, 1.33	0.042	1.20	1.04, 1.38	0.084	1.17	1.01, 1.35	0.201

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for study site, maternal age, race/ethnicity, marital status, insurance, parity, prepregnancy body mass index, preexisting chronic disease, smoking during pregnancy, alcohol consumption during pregnancy, and season of conception. Levels of air toxics were dichotomized at the 75th percentile, and high exposure (≥75th percentile) was compared with the rest of the distribution.

[b] Trimester 1 refers to gestational weeks 1–13.

[c] *P* values were false discovery rate–adjusted within each exposure window.

Netherlands was greater (13), which might be partly explained by the higher levels of PM_{10} exposure than those in our study (whole-gestation mean = 30.7 (standard deviation, 3.9) $\mu g/m^3$ vs. 22.1 (standard deviation, 4.4) $\mu g/m^3$). In a population-based study in New York, New York, despite the positive associations between first- or second-trimester exposures to $PM_{2.5}$ and NO_2 and risk of GH, associations were attenuated toward the null after further adjustment for delivery hospital (26). As discussed by Savitz et al. (26), a relatively large geographic coverage might address the issue of small exposure contrasts, whereas the uncertain validity of adjusting for location-related factors should be recognized, which may partially adjust out the influence of spatial variation. Nonetheless, our findings remain robust even after adjustment for study site and a simulation to consider potential exposure misclassification.

Table 4. Naive and Simulation Extrapolation Estimation of the Association Between Ambient SO_2 Exposure During the First Trimester With Risk Of Gestational Hypertension ($n = 206,054$), Consortium on Safe Labor/Air Quality and Reproductive Health Study, United States, 2002–2008

Estimation Method	Adjusted RR[a]	95% CI
Naive estimation[b]	1.22	1.14, 1.31
Simulation extrapolation estimation (10% measurement error)	1.26	1.16, 1.37
Simulation extrapolation estimation (20% measurement error)	1.28	1.18, 1.40

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for study site, maternal age, race/ethnicity, marital status, insurance, parity, prepregnancy body mass index, preexisting chronic disease, smoking during pregnancy, alcohol consumption during pregnancy, and season of conception.

[b] The naive estimation was based on the same Poisson model reported in Web Table 2, except that we did not account for multiple pregnancies of the same woman, because the simex function in R does not allow clustering. Because most participants contributed only 1 pregnancy (92%), we would expect the inference from Poisson regression to be very close to that from generalized estimating equations (adjusted RR = 1.22, 95% CI: 1.11, 1.34; Web Table 2).

Our novel findings of positive associations between GH risk and SO_2 exposures both before conception and during early gestation address a data gap on this criteria pollutant. In contrast, the positive associations of GH with NO_x and particulate matter were only significant during the early gestation window. Collectively, these data suggest that the associations were more pronounced during early gestation for air pollutants that are primarily from transport emissions (i.e., NO_x and particulate matter), whereas SO_2, a pollutant released mainly during fossil fuel combustion, might have a more chronic and sustained pathway.

Despite the lack of previous epidemiologic data on $PM_{2.5}$ constituents and risk of GH, our novel findings on positive associations of dust particles and elemental carbon with increased risk of GH are biologically plausible. Animal studies suggest that acute cardiovascular dysregulation in response

to $PM_{2.5}$ exposure is driven mostly by elemental carbon and its fractions (28). In addition, concentrated dust-storm particles induce adverse cardiovascular effects on spontaneously hypertensive rats, suggesting its toxic nature (29). Indeed, certain particle constituents may reach the systemic circulation via inhalation, stimulating endothelial dysfunction and vasomotor imbalance via vascular inflammation and oxidative stress (30–32).

Notably, we observed novel, positive associations of GH with air toxics, particularly VOCs before conception. Consistent with our findings, available yet limited data suggest that total VOC exposure is significantly associated with higher levels of blood pressure among overweight/obese individuals (33). In particular, we observed a 17% higher risk of GH associated with preconceptional exposure to toluene, which originates mostly from gasoline/solvent usage, automobile emissions, and paint/varnish/adhesive evaporation (34). Similarly, toluene has been linked to higher blood pressure among synthetic leather workers and drivers (35, 36). In addition, mixed (m-, o-, and p-) xylenes, commonly used industrial products via methylation of toluene and benzene (37), have been linked to adverse reproductive outcomes including fetal resorption, anomalies, and decreased fetal weight in animals (38, 39). Taken together, despite the relatively low exposure levels, the ubiquitous and involuntary nature of these underappreciated exposures to ambient air toxics warrants further investigation in relation to reproductive outcomes. Further, regarding the observed pollutant- and toxic-specific associations, in addition to the limited mechanistic data on particular exposures in relation to the disease outcome as discussed above, these novel findings suggest areas for future investigation to elucidate potential mechanisms beyond overall oxidative stress and inflammatory effects (40).

There are several notable strengths of this study. In this national cohort with both temporal and spatial dispersion, we were able to examine the associations of criteria pollutants and source-specific exposures ($PM_{2.5}$ constituents, PAHs, and VOCs) within specific exposure windows. The ascertainment of outcome and other detailed clinical factors as covariates was based on medical records and hospital discharge data, which may be unavailable or unreliably reported in investigations that use birth certificates or insurance data (41). Further, we accounted for location-related factors by adjusting for study site, which is a common limitation in previous studies as recognized by Pedersen et al. (10) in a recent meta-analysis.

Several limitations of the study should be noted. First, exposure misclassification cannot be ruled out; we used hospital referral region as the geographic unit due to the anonymity of the CSL data. Women may move during the exposure window of interest, although this should be nondifferential by case status. Maternal residential mobility during pregnancy tends to involve short-distance moves with a median of <10 km (42), which would likely leave most women in the same hospital referral region. Further, the simulation extrapolation demonstrated the robustness of the results for SO_2 exposure during the first trimester with a small to moderate measurement error rate. Second, because the dates of diagnoses were not available from the medical records, we were unable to evaluate potential competing risks of other hypertensive disorders of pregnancy and, as such, focus on women who were normotensive throughout pregnancy in comparison with those who had GH at delivery. Because GH occurs after 20 weeks of gestation by definition, we selected exposure windows before week 20 to ensure that the exposure always preceded the outcome. Furthermore, although the etiology of GH remains to be confirmed, this pregnancy complication is believed to begin in early pregnancy, when important events including placentation and organogenesis occur. Third, given that our cohort was compiled during 2002–2008, more recent data applying the new definition of hypertensive disorders during pregnancy by the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy (43) are warranted to confirm our findings. In particular, the impact of classifying new-onset hypertension without proteinuria, but with new onset of other symptoms, as preeclampsia (which could have been diagnosed as GH by the old definition) is yet to be assessed. Finally, we could not completely rule out the possibility of findings due to chance given the potential multiplicity issue, despite the false discovery rate adjustment. However, the number of significant associations with a consistent direction may suggest a pattern of findings beyond chance.

In conclusion, our findings based on a large, contemporary nationwide cohort suggest that early pregnancy is a critical exposure window particularly for transport emission–related pollutants (NO_x, $PM_{2.5}$, and PM_{10}) in relation to risk of GH. In addition, SO_2 exposure both before conception and during early gestation illustrated a consistent pattern of 18%–22% higher risk of GH. Further, several air toxics, particularly greater levels of several VOCs and some PAHs during the 3 months before conception, were significantly associated with higher risk of GH. The potential chronic impact of these air toxics associated with preconceptional exposures on reproductive outcomes warrants further investigation.

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