Ambient Fine Particulate Matter, Nitrogen Dioxide, and Hypertensive Disorders of Pregnancy in New York City

David A. Savitz,[a] *Beth Elston,*[b] *Jennifer F. Bobb,*[c] *Jane E. Clougherty,*[d] *Francesca Dominici,*[c] *Kazuhiko Ito,*[e] *Sarah Johnson,*[e] *Tara McAlexander,*[e] *Zev Ross,*[f] *Jessie L. C. Shmool,*[d] *Thomas D. Matte,*[e] *and Gregory A. Wellenius*[b]

Background: Previous studies suggested a possible association between fine particulate matter air pollution ($PM_{2.5}$) and nitrogen dioxide (NO_2) and the development of hypertensive disorders of pregnancy, but effect sizes have been small and methodologic weaknesses preclude firm conclusions.

Methods: We linked birth certificates in New York City in 2008–2010 to hospital discharge diagnoses and estimated air pollution exposure based on maternal address. The New York City Community Air Survey provided refined estimates of $PM_{2.5}$ and NO_2 at the maternal residence. We estimated the association between exposures to $PM_{2.5}$ and NO_2 in the first and second trimester and risk of gestational hypertension, mild preeclampsia, and severe preeclampsia among 268,601 births.

Results: In unadjusted analyses, we found evidence of a positive association between both pollutants and gestational hypertension. However, after adjustment for individual covariates, socioeconomic deprivation, and delivery hospital, we did not find evidence of an association between $PM_{2.5}$ or NO_2 in the first or second trimester and any of the outcomes.

Conclusions: Our data did not provide clear evidence of an effect of ambient air pollution on hypertensive disorders of pregnancy. Results need to be interpreted with caution considering the quality of the available exposure and health outcome measures and the uncertain impact of adjusting for hospital. Relative to previous studies, which have tended to identify positive associations with $PM_{2.5}$ and NO_2, our large study size, refined air pollution exposure estimates, hospital-based disease ascertainment, and little risk of confounding by socioeconomic deprivation, does not provide evidence for an association.

(*Epidemiology* 2015;26: 748–757)

Over the past decade, evidence has accumulated suggesting that air pollution, especially fine particulate matter (particulate matter with aerodynamic diameter less than or equal to 2.5 µm, $PM_{2.5}$), and nitrogen dioxide (NO_2) may be related to adverse pregnancy outcomes. While the evidence is most extensive for a possible influence on fetal growth and timing of delivery,[1] there is a growing literature addressing hypertensive disorders of pregnancy, which include preeclampsia (pregnancy-induced hypertension with proteinuria) and gestational hypertension (pregnancy-induced hypertension without proteinuria).[2] These complications of pregnancy are common (2%–5% of births), with higher prevalence in first births and among obese women, and only resolve with delivery.[3] Observations of weak associations of air pollution with birth weight and preterm birth may be accounted for in part by an impact of air pollution on hypertensive disorders, which are associated with those adverse birth outcomes. If this were the primary pathway linking air pollution to preterm birth, then the association of air pollution directly with hypertensive disorders would have to be stronger than the association between air pollution and preterm birth.

A large body of evidence suggests that air pollution can induce systemic inflammation, oxidative stress, and vascular endothelial injury[4,5]—the same mechanisms hypothesized to cause preeclampsia.[6,7] Thus, while there is not a well-established pathophysiologic pathway linking ambient air pollution to preeclampsia, an association is biologically plausible. Several studies have reported positive associations between $PM_{2.5}$ and hypertensive disorders of pregnancy[8–14] or elevations in mean blood pressure in pregnancy,[15,16] but effect sizes have tended to be quite small and other studies of similar design and quality have not found positive associations.[17] In recent meta-analyses, Pedersen et al.[2] reported a combined odds

Submitted 16 October 2014; accepted 26 May 2015.

From the [a]Departments of Epidemiology and Obstetrics and Gynecology, Brown University, Providence, RI; [b]Department of Epidemiology, Brown University, Providence, RI; [c]Department of Biostatistics, Harvard School of Public Health, Boston, MA; [d]Department of Occupational and Environmental Health, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; [e]New York City Department of Health and Mental Hygiene, New York, NY; and [f]ZevRoss Spatial Analysis, Ithaca, NY.

Supported by Grants R01-ES019955 and R21-ES023073 from the National Institute of Environmental Health Sciences. The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the sponsoring institutions.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com). This content is not peer-reviewed or copy-edited; it is the sole responsibility of the authors.

Correspondence: David A. Savitz, Brown University, 47 George Street, 3rd Floor, Room 302, Providence, RI 02912. E-mail:david_savitz@brown.edu.

ISSN: 1044-3983/15/2605-0748
DOI: 10.1097/EDE.0000000000000349

ratio of 1.57 (95% confidence interval [CI] = 1.26, 1.96) per 5 μg/m^3 $PM_{2.5}$ for all hypertensive diseases of pregnancy, whereas Hu et al.[18] found a combined odds ratio of 1.18 (95% CI = 0.98, 1.41) per 5 μg/m^3 for exposure in the first trimester and similar results for the second trimester. The differences in results may be explained by slight differences in inclusion criteria affecting one study[17] and use of full pregnancy exposure[2] versus first/second trimester exposure only.[18] The literature on NO_2, a marker of traffic-related air pollution, is less extensive but includes a number of positive reports,[8,11,19,20] as well as null findings.[12,21,22] In their meta-analysis, Pedersen et al.[2] estimated a combined odds ratio for NO_2 of 1.41 (95% CI = 1.00, 1.98) per 10 ppb for all hypertensive disorders of pregnancy combined, in contrast to Hu et al.[18] who reported a combined odds ratio of 1.05 (95% CI = 0.99, 1.12) per 10 ppb for exposure in the first trimester and similar results for second-trimester exposure.

Previous studies have generally been limited in one or more of the following key features: quality of exposure assessment (relying on sparse regulatory air pollution monitoring data), quality of outcome assessment (often relying on birth certificate data), or limited study size (clinical populations with relatively small numbers of cases). We examined the association of $PM_{2.5}$ and NO_2 with hypertensive disorders of pregnancy employing data from a unique urban air monitoring program designed to assess intra-urban variation in population exposures, and to draw on a combination of birth certificate and hospital discharge diagnoses for a large, diverse population of pregnant women across New York City. In a previous analysis of data from this study, residential concentrations of these two air pollutants were associated with a small decrement in birth weight,[23] calling for an examination of the hypothesis that this finding might be accounted for by a more marked association with hypertensive disorders.

MATERIALS AND METHODS

Study Population

Birth records of 348,585 live births to residents of New York City occurring in New York City hospitals during the years 2008–2010 (Figure 1) were available for analysis, excluding the estimated 4% of live births to New York residents that occurred at hospitals outside New York City (reported in detail in a previous publication).[23] We linked birth certificate files to hospital discharge data provided by the New York State Department of Health Statewide Planning and Research Cooperative System, which included information on medical conditions before and during pregnancy. We restricted the study to singleton births to nonsmoking mothers (based on birth certificate data) given the established inverse association between smoking and hypertensive disorders in pregnancy,[24] the challenge of isolating the impact of air pollution in the presence of active smoking, and the limited detail available in our data on intensity of smoking. We also excluded mothers diagnosed with prepregnancy hypertension based on hospital discharge data. To avoid the fixed cohort bias and to obtain a cohort defined by conception rather than by birth date with consistent distributions of gestational age across calendar time,[25] we excluded births with an estimated date of conception before July 31, 2007 (i.e., 22 weeks before January 1, 2008) or after March 12, 2010 (i.e., 42 weeks before December 31, 2010). We also excluded those missing residential address information needed for estimating exposure, implausible birth weights (<500 or >5,000 g), and missing outcome or covariate information, less than 5% of the remaining population after exclusions noted above (Figure 1). While there is information on hypertensive conditions in both the birth certificate and the hospital discharge data, previous studies have indicated that hospital discharge data are superior[26] and this source allows for subdivision into mild and severe preeclampsia and gestational hypertension that is not possible with birth certificate information alone. After the above exclusions, our population included 268,601 births. Analyses that adjusted for delivery hospital were further restricted to include records which had such information and only included hospitals with 10 or more births per outcome, leaving 262,946 births at 41 hospitals. The protocol was reviewed and approved by the New York City Department of Health and Mental Hygiene Institutional Review Board.

Exposure Assessment

The method for assigning $PM_{2.5}$ and NO_2 exposures to each birth at the mother's birth residence has been described elsewhere.[23,27] In brief, the method consists of estimating the citywide spatial variation of air pollutants followed by temporal adjustment of the spatial data to match gestational exposure time windows. As part of the New York City Community Air Survey,[28,29] 2-week average concentrations at street level (~3–4 m off the ground) of several pollutants, including $PM_{2.5}$ and NO_2, were measured at 150 monitoring sites in each of the four seasons for the period December 2008 to December 2010. We used the measurements collected during December 2008–December 2009 (i.e., Year 1 New York City Community Air Survey data) to fit spatial models for each pollutant as described below. Then the spatiotemporal model was validated by estimating 2-week average measurements for December 2009–December 2010 (Year 2 data) and comparing them with the actual measurements.

We used geographic information systems to compute emissions and land use variables within buffer regions around each monitoring location.[27,28] Each of these variables was tested for inclusion in regression models predicting the pollutant annual average concentrations. The final regression models included the strongest predictor variables and were extended to account for residual spatial autocorrelation using kriging with external drift. We applied the models to generate a surface of estimated average pollutant concentrations across the 790 km^2 of the city which was used to construct

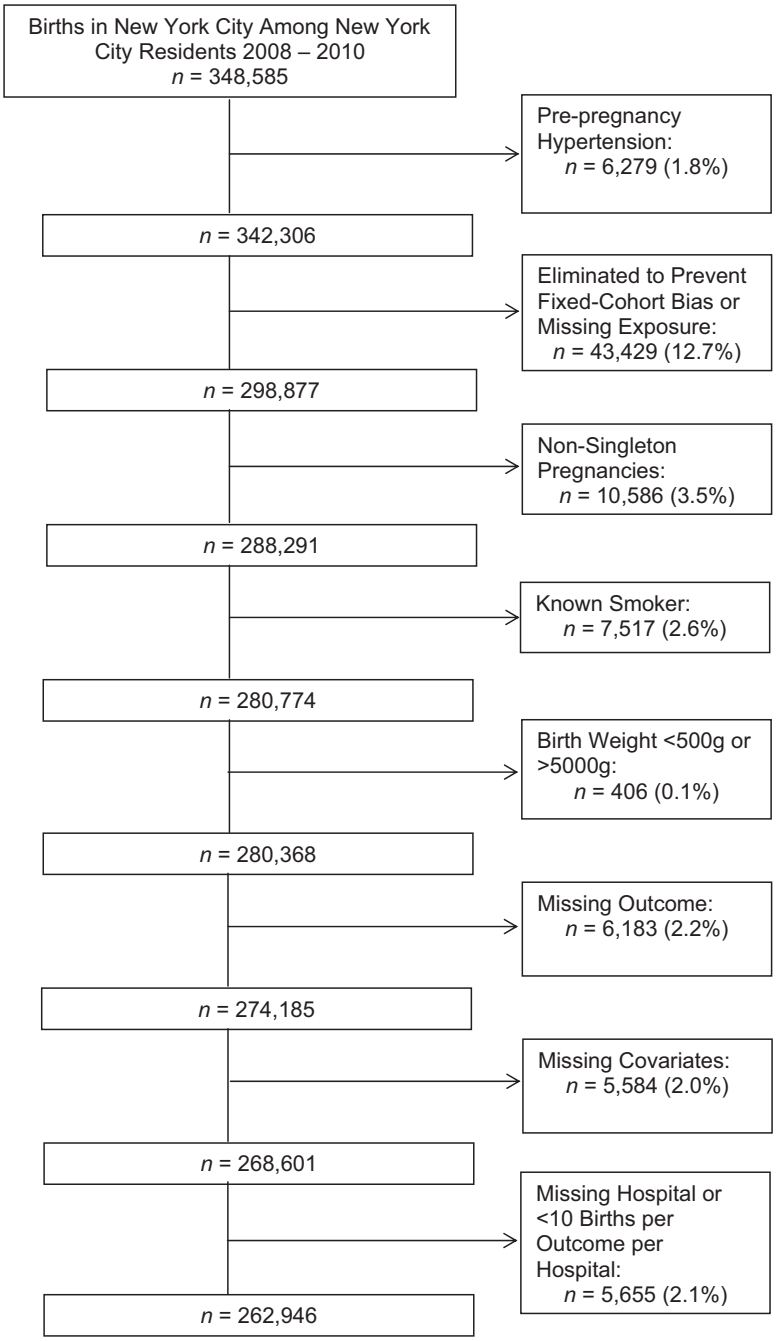

FIGURE 1. Exclusions for analysis of air pollution exposure and hypertensive disorders of pregnancy, New York City, 2008–2010.

exposure estimates within 300 m of each maternal address at the time of delivery based on the birth certificate. The spatial exposure surface described above (based on annual average concentrations) was then temporally adjusted to match pregnancy time windows using a city-wide time series computed from continuous regulatory monitors. The R^2 value for predictions of 2-week average concentrations of $PM_{2.5}$ and NO_2 against actual concentrations measured during December 2009–December 2010 at the 150 New York City Community Air Survey distributed sites was 0.83 and 0.79, respectively. To the best of our knowledge, there was no major change in the spatial pattern of emission sources in New York City over the relatively brief time interval of the study that would have substantially impacted the relative spatial distribution of these pollutants during the study period, and the validation results in part support this inference.

Pregnancy Outcome and Covariates

We examined the association of air pollution with hypertensive disorders of pregnancy in four case groups, defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge diagnoses: (1)

all hypertensive disorders of pregnancy (ICD-9-CM Codes: 642.30–642.34, 642.90–642.94, 642.40–642.44, 642.50–642.54, and 642.60–642.64); (2) gestational hypertension only (ICD-9-CM codes: 642.30–642.34 and 642.90–642.94); (3) mild preeclampsia (ICD-9-CM codes: 642.40–642.44), and (4) severe preeclampsia/eclampsia (ICD-9-CM Codes: 642.50–642.54 and 642.60–642.64). In each case, the referent group consisted of women with no diagnosis of hypertension. In cases where a woman had codes for more than one of the categories of hypertensive disorders, we assigned her exclusively to the diagnosis reflecting the most severe form, ordered as severe preeclampsia/eclampsia, mild preeclampsia, and gestational hypertension. In a sensitivity analysis, we also considered duration of gestation based on clinical estimates (which typically incorporate ultrasound information), examining pregnancies resulting in preterm births (<37 weeks gestational age) with hypertensive disorder, and term pregnancies with hypertensive disorder, each compared with pregnancies with no hypertensive disorder.

We adjusted for the following covariates known or suspected to be associated with one or more of the above hypertensive disorders: maternal age (<20, 20–24, 25–29, 30–34, 35–39, ≥40), race/ethnicity (non-Hispanic white, black, Hispanic, Asian, or other/unknown), education (<9, 9–11, 12, 13–15, 16, or >16 years), parity (0, 1, or ≥2), conception year (2007, 2008, 2009, 2010), body mass index (BMI), BMI^2, and Medicaid status (no/yes), identifying women of low income who qualified for this program. To address potential confounding by contextual socioeconomic status, we developed a social deprivation index based on the US census tract containing the address listed on the birth certificate (mean = 118 births/tract). We adapted the approach of Messer et al.,[30] using principal components analysis to derive a composite index, which included the following seven contextual variables: percent with college degree, percent unemployment, percent management/professional occupation, percent residential crowding, percent below 200% of the federal poverty line, percent of households receiving public assistance, and percent nonwhite race. To control for hospital-specific effects, we also adjusted for delivery hospital as a categorical variable.

Statistical Analysis

We estimated the associations between individual-level estimated exposures to $PM_{2.5}$, NO_2, and the specific hypertensive disorders of pregnancy using multinomial logistic regression, with the referent group consisting of women not diagnosed with a hypertensive disease during pregnancy. We considered exposure in the first trimester (weeks 1–12) and second trimester (weeks 13–26) of pregnancy in separate models. For each exposure window and each pollutant ($PM_{2.5}$ and NO_2), we initially considered three models: (1) unadjusted; (2) adjusted for all of the individual-level covariates described above and the census tract social deprivation index; and (3) adjusted for all covariates noted previously plus a categorical variable for the delivery hospital. Given our reliance on discharge diagnoses in administrative databases, identification as a case depends on the completeness and specificity of coding, which may vary across hospitals. Because adjustment for delivery hospital had a material effect on some of the results, and because there is uncertainty regarding which is the more valid estimate, findings from models including and excluding adjustment for delivery hospital are presented.

We analyzed continuous measures of $PM_{2.5}$ and NO_2, with results expressed as odds ratios per 10 $\mu g/m^3$ $PM_{2.5}$ and 10 ppb NO_2, respectively. In the categorical analysis, exposure quartiles 2, 3, and 4 were contrasted with quartile 1 as the referent. We assessed the linear trend in the quartile-specific odds ratios estimated from these models using the Cochran-Armitage test. We conducted several sensitivity analyses, including isolating spatial and temporal contributors to exposure, mutually adjusting for the same pollutant in alternate trimesters, mutually adjusting for $PM_{2.5}$ and NO_2 in the same trimester, adjusting for season, excluding those with pre-existing diabetes, gestational diabetes or pre-existing kidney disease, restricting to nulliparous women, including hospital as a random effect rather than a fixed effect, and using an alternative outcome which incorporated term and preterm births as described above. Analyses were performed using SAS 9.3 (Cary, NC).

RESULTS

The study population reflects New York City's ethnic and socioeconomic diversity (Table 1). Half the population was Black or Hispanic, half had 12 or fewer years of education, and over half received Medicaid assistance. Distribution of births by year was uneven due to truncation at the beginning and end to avoid the fixed cohort bias.[25] Higher risk of hypertensive disorders was seen for the youngest and oldest mothers, for Black and Hispanic women (relative to non-Hispanic whites), and for women with lower education or living in areas of greater socioeconomic deprivation. The social deprivation variable had a weak negative linear association with the pollutants (Pearson correlation coefficients at the census-tract level of −0.11 and −0.07 for $PM_{2.5}$ and NO_2, respectively). Nulliparous women and women with higher BMI had a markedly increased risk of hypertensive disorders. Differences in predictors of risk for the different hypertensive disorders were modest.

In models not adjusted for delivery hospital, $PM_{2.5}$ in the first and second trimesters of pregnancy was positively related to risk of gestational hypertension and inversely related to risk of mild preeclampsia (Figure 2, Table 2, eTable 1; http://links.lww.com/EDE/A938). Specifically, in the highest quartile of exposure, the adjusted odds ratios for gestational hypertension were 1.4 (95% CI = 1.2, 1.5) in the first trimester and 1.4 (95% CI = 1.3, 1.5) in the second trimester. Additional adjustment for delivery hospital essentially eliminated these associations, and in either model, $PM_{2.5}$ was unrelated to total hypertensive disorders or severe preeclampsia.

TABLE 1. Sociodemographic Characteristics and Hypertensive Diseases of Pregnancy, New York City, 2008–2010

	All Pregnancies	Total Hypertensive Disorders	Gestational Hypertension	Mild Preeclampsia	Severe Preeclampsia/ Eclampsia
Characteristic	**n (%)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Total[a]	268,601	17,000 (6.3)	5,834 (2.2)	6,940 (2.6)	4,226 (1.6)
Maternal age					
<20	17,972 (6.7)	1.9 (1.8, 2.0)	1.5 (1.4, 1.7)	2.1 (1.9, 2.3)	2.0 (1.8, 2.3)
20–24	56,088 (21)	1.2 (1.2, 1.3)	1.1 (0.99, 1.2)	1.3 (1.2, 1.4)	1.2 (1.1, 1.3)
25–29	71,468 (27)	1.0	1.0	1.0	1.0
30–34	70,674 (26)	0.96 (0.91, 1.0)	1.0 (0.95, 1.1)	0.89 (0.83, 0.96)	0.96 (0.87, 1.0)
35–39	40,802 (15)	1.1 (1.1, 1.2)	1.2 (1.1, 1.3)	1.0 (0.92, 1.1)	1.2 (1.1, 1.4)
≥40	11,597 (4.3)	1.5 (1.4, 1.7)	1.6 (1.5, 1.9)	1.3 (1.1, 1.4)	1.8 (1.6, 2.1)
Maternal ethnicity					
Non-Hispanic White	75,362 (28)	1.0	1.0	1.0	1.0
Black	57,052 (21)	2.5 (2.4, 2.6)	1.8 (1.6, 1.9)	2.9 (2.7, 3.1)	3.1 (2.8, 3.4)
Hispanic	90,305 (34)	1.8 (1.7, 1.9)	1.4 (1.3, 1.5)	2.0 (1.8, 2.1)	2.3 (2.1, 2.5)
Asian	40,215 (15)	0.83 (0.78, 0.88)	0.72 (0.65, 0.79)	0.88 (0.80, 0.98)	0.96 (0.84, 1.1)
Unknown/other	5,667 (2.1)	1.3 (1.2, 1.5)	1.1 (0.92, 1.4)	1.2 (1.0, 1.5)	1.9 (1.5, 2.4)
Maternal education					
<9	21,826 (8.1)	1.1 (1.0, 1.1)	0.93 (0.82, 1.0)	1.0 (0.93, 1.1)	1.3 (1.2, 1.5)
9–11	47,617 (18)	1.2 (1.1, 1.2)	1.2 (1.1, 1.3)	1.2 (1.1, 1.2)	1.2 (1.1, 1.3)
12	64,570 (24)	1.0	1.0	1.0	1.0
13–15	58,729 (22)	1.2 (1.2, 1.3)	1.3 (1.2, 1.5)	1.1 (1.0, 1.2)	1.2 (1.1, 1.3)
16	43,316 (16)	0.89 (0.85, 0.94)	1.2 (1.1, 1.3)	0.70 (0.65, 0.76)	0.81 (0.73, 0.90)
>16	32,543 (12)	0.81 (0.77, 0.86)	1.1 (1.0, 1.2)	0.62 (0.56, 0.68)	0.78 (0.69, 0.88)
Medicaid					
No	104,120 (39)	0.84 (0.81, 0.87)	1.1 (1.0, 1.1)	0.71 (0.67, 0.74)	0.80 (0.75, 0.85)
Yes	164,481 (61)	1.0	1.0	1.0	1.0
Parity					
0	125,411 (47)	1.0	1.0	1.0	1.0
1	78,911 (29)	0.48 (0.47, 0.50)	0.51 (0.48, 0.55)	0.47 (0.44, 0.50)	0.48 (0.44, 0.51)
≥2	64,279 (24)	0.55 (0.53, 0.58)	0.59 (0.55, 0.63)	0.52 (0.49, 0.56)	0.56 (0.51, 0.60)
Conception year					
2007	44,270 (16)	1.0 (0.96, 1.1)	0.99 (0.92, 1.1)	1.0 (0.96, 1.1)	1.0 (0.92, 1.1)
2008	103,189 (38)	1.0	1.0	1.0	1.0
2009	101,047 (38)	1.0 (1.0, 1.1)	1.0 (0.98, 1.1)	1.0 (0.98, 1.1)	1.1 (0.99, 1.1)
2010	20,095 (7.5)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.0 (0.93, 1.1)	1.2 (1.0, 1.3)
Deprivation index[b]	0.36 (−0.46, 1.0)	1.2 (1.2, 1.2)	1.1 (1.1, 1.1)	1.2 (1.2, 1.3)	1.2 (1.2, 1.2)
BMI (kg/m^2)					
Underweight (<18.5)	15,083 (5.6)	0.72 (0.65, 0.78)	0.68 (0.58, 0.80)	0.74 (0.64, 0.85)	0.72 (0.61, 0.86)
Normal (18.5 to <25)	146,336 (54)	1.0	1.0	1.0	1.0
Overweight (25 to <30)	63,801 (24)	1.7 (1.6, 1.7)	1.7 (1.6, 1.9)	1.7 (1.6, 1.8)	1.5 (1.4, 1.6)
Obese (≥30)	43,381 (16)	2.7 (2.6, 2.8)	2.9 (2.7, 3.1)	2.8 (2.6, 3.0)	2.2 (2.0, 2.4)

[a]n (%).
[b]Median ($Q1$, $Q3$).

We observed a similar pattern of results for NO_2 (Figure 3, Table 2, eTable 2; http://links.lww.com/EDE/A938), with a clear positive gradient in risk of gestational hypertension and a negative gradient for mild preeclampsia in models without hospital adjustment. This was the case for both first- and second-trimester exposures. In models without hospital adjustment, second-trimester NO_2 exposures were associated with a slight increase in total hypertensive disorders and severe preeclampsia, although both associations were eliminated with hospital adjustment.

We conducted a series of sensitivity analyses to further understand the pattern of results (Table 3, eTable 3; http://links.lww.com/EDE/A938). Examining only spatial variation in pollutants as the exposure measure markedly enhanced

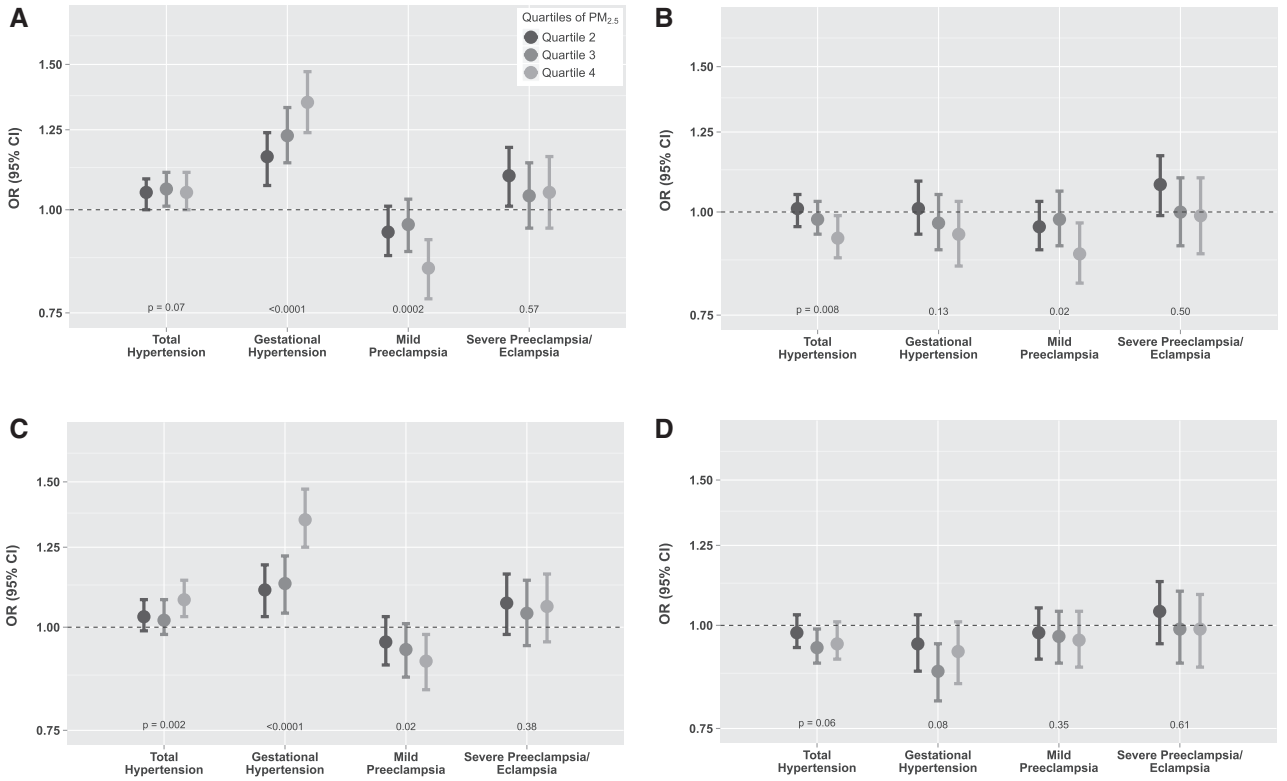

FIGURE 2. Association between quartiles of $PM_{2.5}$ levels and hypertensive disorders of pregnancy. A, First trimester standard adjustment; (B) first trimester standard with hospital adjustment; (C) second trimester standard adjustment; (D) second trimester standard with hospital adjustment. *P* value from Cochran-Armitage test for linear trend noted.

the positive association with gestational hypertension and inverse association for mild preeclampsia without hospital adjustment, for $PM_{2.5}$. Temporal variation in both pollutants in both trimesters, with or without hospital adjustment was not associated with any of the outcomes. Mutual adjustment of $PM_{2.5}$ for NO_2 and vice versa attenuated the results for each somewhat without hospital adjustment and had little effect on the results with hospital adjustment. Adjustment for the same pollutant in the other trimester had little impact as did adjustment for season of birth and restriction to women without preexisting diabetes, gestational diabetes, or preexisting kidney disease with or without hospital adjustment. Including hospital as a random rather than fixed effect had little impact on the results. The associations were attenuated when the outcome was restricted to preterm birth with hypertensive disorders without adjustment for hospital (eTable 4; http://links.lww.com/EDE/A938).

Hospital was a positive confounder for the association between each pollutant and gestational hypertension, and a negative confounder for their associations with mild preeclampsia (Table 2, eTable 5; http://links.lww.com/EDE/A938). This was the general pattern for both $PM_{2.5}$ and NO_2, first and second trimester, and driven by the spatial variation in exposure as would be expected, given that delivery hospital is largely a spatial variable.

DISCUSSION

In a study built on a thorough assessment of air pollution exposures across New York City, with hospital discharge data on diagnoses, we generally found a lack of evidence of a positive association between either $PM_{2.5}$ or NO_2 and hypertensive disorders of pregnancy except for gestational hypertension in models without adjustment for hospital. Confounding by socioeconomic status is a major concern in most settings;[31] but in New York City, indicators of social deprivation are generally weakly negatively correlated with these air pollutants (eTable 6; http://links.lww.com/EDE/A938).[32] Given the null results after adjusting for delivery hospital, it is important to ask whether there are aspects of the study that could have generated spurious null findings in the presence of a true association.

Although it is possible that there is a true effect of pollution on the occurrence of hypertensive disorders that is pronounced enough to be reflected in the varying rates of hypertensive disorders across hospitals (as shown in eTable 5; http://links.lww.com/EDE/A938), we believe that these apparent associations may be due to institution-level differences in disease coding and diagnosis. The pattern of compensating increased gestational hypertension and reduced mild preeclampsia, with little overall association for total hypertensive disorders, makes the potential for variation in coding across

TABLE 2. Odds Ratios of $PM_{2.5}$ and NO_2 with Hypertensive Disorders by Trimester, Unadjusted, Standard Adjustment, and Standard Adjustment Plus Adjustment for Hospital: New York City, 2008–2010

	Total Hypertensive Disorders (n = 17,000)	Gestational Hypertension Only (n = 5,834)	Mild Preeclampsia (n = 6,940)	Severe Preeclampsia/ Eclampsia (n = 4,226)
Exposure/Model	**OR[a] (95% CI)**	**OR[a] (95% CI)**	**OR[a] (95% CI)**	**OR[a] (95% CI)**
$PM_{2.5}$[a]				
First trimester				
Unadjusted	0.98 (0.92, 1.0)	1.4 (1.2, 1.5)	0.76 (0.69, 0.84)	0.91 (0.81, 1.0)
Standard adjustment[b]	1.1 (1.0, 1.2)	1.7 (1.5, 1.9)	0.82 (0.73, 0.92)	1.1 (0.91, 1.2)
Standard adjustment[b] + adjustment for hospital	0.93 (0.86, 1.0)	0.97 (0.86, 1.1)	0.88 (0.78, 1.0)	0.95 (0.82, 1.1)
Second trimester				
Unadjusted	1.0 (0.93, 1.1)	1.4 (1.2, 1.5)	0.77 (0.69, 0.85)	0.95 (0.84, 1.1)
Standard adjustment[b]	1.1 (1.0, 1.2)	1.6 (1.4, 1.8)	0.8 (0.7, 0.9)	1.1 (0.93, 1.3)
Standard adjustment[b] + adjustment for hospital	0.91 (0.84, 0.99)	0.88 (0.77, 1.0)	0.91 (0.80, 1.0)	0.96 (0.81, 1.1)
NO_2[c]				
First trimester				
Unadjusted	0.98 (0.96, 1.0)	1.1 (1.1, 1.2)	0.86 (0.82, 0.89)	0.99 (0.94, 1.0)
Standard adjustment[b]	1.0 (1.0, 1.1)	1.2 (1.2, 1.3)	0.89 (0.85, 0.93)	1.0 (0.98, 1.1)
Standard adjustment[b] + adjustment for hospital	0.93 (0.90, 0.96)	0.95 (0.90, 1.0)	0.89 (0.84, 0.93)	0.96 (0.90, 1.0)
Second trimester				
Unadjusted	0.99 (0.97, 1.0)	1.2 (1.1, 1.2)	0.89 (0.85, 0.92)	0.95 (0.90, 1.0)
Standard adjustment[b]	1.1 (1.0, 1.1)	1.3 (1.2, 1.4)	0.93 (0.89, 0.98)	1.0 (0.97, 1.1)
Standard adjustment[b] + adjustment for hospital	0.96 (0.93, 0.99)	1.0 (0.95, 1.1)	0.94 (0.89, 0.99)	0.93 (0.87, 0.99)

[a]Estimates are for each 10 μg/m^3 increase of $PM_{2.5}$.
[b]Adjusted for maternal age, maternal ethnicity, maternal education, Medicaid status, parity, conception year, deprivation index, BMI, BMI2.
[c]Estimates are for each 10 ppb increase of NO_2.

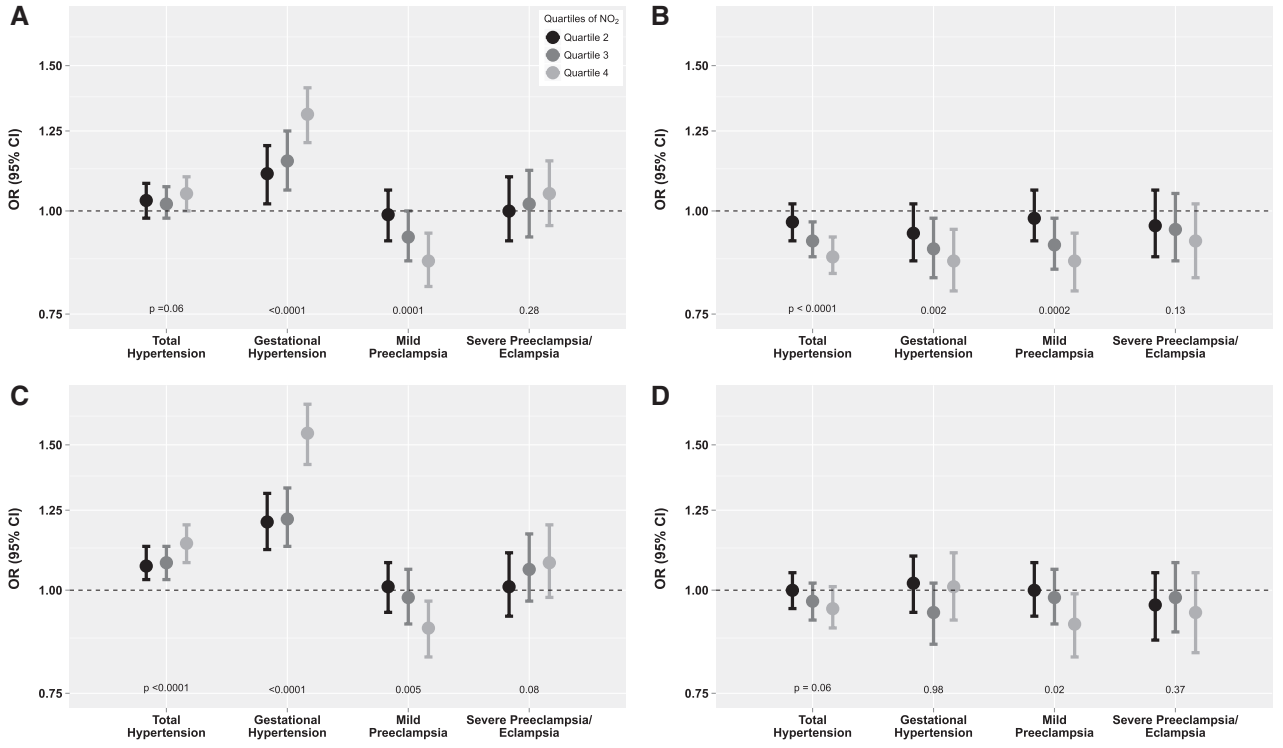

FIGURE 3. Association between quartiles of NO_2 levels and hypertensive disorders of pregnancy. A, First trimester standard adjustment; (B) first trimester standard with hospital adjustment; (C) second trimester standard adjustment; (D) second trimester standard with hospital adjustment. *P* value from Cochran-Armitage test for linear trend noted.

TABLE 3. Sensitivity Analyses for Varying Restrictions, Exposure, and Covariates Using Continuous Measure of Exposure and Standard Adjustment Unless Otherwise Noted, New York City, 2008–2010

	Total Hypertensive Disorders (n = 17,000)	Gestational Hypertension (n = 5,834)	Mild Preeclampsia (n = 6,940)	Severe Preeclampsia (n = 4,226)
Exposure/Model	**OR[a] (95% CI)**	**OR[a] (95% CI)**	**OR[a] (95% CI)**	**OR[a] (95% CI)**
$PM_{2.5}$[b]				
Spatial only[c]	1.4 (1.3, 1.6)	3.6 (3.0, 4.4)	0.64 (0.52, 0.78)	1.1 (0.90, 1.5)
Spatial only[c] with hospital adjustment	0.85 (0.73, 0.98)	0.95 (0.76, 1.2)	0.76 (0.59, 0.97)	0.83 (0.62, 1.1)
First trimester				
Temporal only[d]	0.97 (0.87, 1.1)	0.97 (0.81, 1.1)	0.94 (0.80, 1.1)	1.0 (0.83, 1.2)
Temporal only[d] with hospital adjustment	0.97 (0.87, 1.1)	0.97 (0.82, 1.2)	0.94 (0.80, 1.1)	1.0 (0.84, 1.3)
Adjusted for NO_2[e]	1.1 (0.99, 1.2)	1.4 (1.2, 1.6)	0.94 (0.82, 1.1)	0.99 (0.83, 1.2)
Adjusted for $PM_{2.5}$ 2nd trimester[f]	1.1 (1.0, 1.2)	1.6 (1.4, 1.8)	0.82 (0.73, 0.92)	1.0 (0.90, 1.2)
Adjusted for season	1.1 (1.1, 1.2)	1.7 (1.5, 2.0)	0.81 (0.72, 0.91)	1.1 (0.91, 1.2)
Exclude those with pre-existing diabetes, gestational diabetes, or pre-existing kidney disease	1.1 (1.1, 1.2)	1.7 (1.5, 1.9)	0.81 (0.72, 0.92)	1.1 (0.93, 1.3)
Restrict to nulliparous women	1.1 (1.0, 1.3)	1.7 (1.5, 2.0)	0.81 (0.70, 0.93)	1.1 (0.89, 1.3)
Second trimester				
Temporal only[d]	0.95 (0.85, 1.1)	0.83 (0.68, 1.0)	1.0 (0.85, 1.2)	1.0 (0.84, 1.3)
Temporal only[d] with hospital adjustment	0.94 (0.84, 1.1)	0.81 (0.67, 0.98)	1.0 (0.84, 1.2)	1.0 (0.83, 1.3)
Adjusted for NO_2[e]	1.0 (0.94, 1.1)	1.2 (1.0, 1.4)	0.89 (0.77, 1.0)	1.1 (0.89, 1.3)
Adjusted for $PM_{2.5}$ 1st trimester[f]	1.1 (1.0, 1.2)	1.5 (1.4, 1.7)	0.85 (0.75, 0.96)	1.1 (0.92, 1.2)
Adjusted for season	1.2 (1.1, 1.3)	1.7 (1.5, 1.9)	0.86 (0.76, 0.97)	1.1 (0.91, 1.2)
Exclude those with pre-existing diabetes, gestational diabetes, or pre-existing kidney disease	1.2 (1.1, 1.3)	1.7 (1.5, 1.9)	0.85 (0.75, 0.97)	1.1 (0.93, 1.3)
Restrict to nulliparous women	1.1 (1.0, 1.2)	1.6 (1.4, 1.9)	0.83 (0.72, 0.97)	1.1 (0.88, 1.3)
NO_2[g]				
Spatial only[c]	1.1 (1.1, 1.1)	1.4 (1.3, 1.5)	0.90 (0.85, 0.95)	1.1 (0.99, 1.1)
Spatial only[c] with hospital adjustment	0.93 (0.89, 0.97)	0.96 (0.90, 1.0)	0.90 (0.83, 0.96)	0.92 (0.84, 1.0)
First trimester				
Temporal only[d]	0.91 (0.85, 0.97)	0.89 (0.80, 0.99)	0.86 (0.78, 0.95)	1.0 (0.91, 1.2)
Temporal only[d] with hospital adjustment	0.90 (0.85, 0.96)	0.88 (0.80, 0.98)	0.85 (0.78, 0.94)	1.0 (0.91, 1.2)
Adjusted for $PM_{2.5}$[e]	1.0 (0.99, 1.1)	1.1 (1.1, 1.2)	0.90 (0.86, 0.95)	1.0 (0.97, 1.1)
Adjusted for NO_2 2nd trimester[f]	0.99 (0.95, 1.0)	1.1 (1.0, 1.1)	0.89 (0.84, 0.94)	1.0 (0.97, 1.1)
Adjusted for season	1.1 (1.0, 1.1)	1.3 (1.3, 1.4)	0.90 (0.86, 0.95)	1.0 (0.98, 1.1)
Exclude those with pre-existing diabetes, gestational diabetes, or pre-existing kidney disease	1.1 (1.0, 1.1)	1.2 (1.2, 1.3)	0.90 (0.85, 0.94)	1.1 (1.0, 1.1)
Restrict to nulliparous women	1.0 (1.0, 1.1)	1.2 (1.2, 1.3)	0.88 (0.84, 0.93)	1.0 (0.94, 1.1)
Second trimester				
Temporal only[d]	1.0 (0.96, 1.1)	1.1 (0.96, 1.2)	1.1 (0.94, 1.2)	0.95 (0.82, 1.1)
Temporal only[d] with hospital adjustment	1.0 (0.96, 1.1)	1.1 (0.96, 1.2)	1.0 (0.94, 1.2)	0.94 (0.82, 1.1)
Adjusted for $PM_{2.5}$[e]	1.1 (1.0, 1.1)	1.3 (1.2, 1.3)	0.96 (0.90, 1.0)	1.0 (0.94, 1.1)
Adjusted for NO_2 1st trimester[f]	1.1 (1.0, 1.1)	1.2 (1.2, 1.3)	1.0 (0.95, 1.1)	1.0 (0.92, 1.1)
Adjusted for season	1.1 (1.1, 1.1)	1.4 (1.3, 1.4)	0.92 (0.87, 0.97)	1.0 (0.97, 1.1)
Exclude those with pre-existing diabetes, gestational diabetes, or pre-existing kidney disease	1.1 (1.1, 1.1)	1.3 (1.3, 1.4)	0.94 (0.90, 0.99)	1.1 (1.0, 1.1)
Restrict to nulliparous women	1.1 (1.0, 1.1)	1.3 (1.2, 1.3)	0.91 (0.86, 0.97)	1.0 (0.95, 1.1)

[a]Adjusted for maternal age, maternal ethnicity, maternal education, Medicaid status, parity, conception year, deprivation index, BMI, BMI^2.
[b]Estimates are for each 10 $\mu g/m^3$ increase of $PM_{2.5}$.
[c]Spatial component of the exposure estimate only.
[d]Temporal component of the exposure estimate only.
[e]Additional adjustment for the other exposure variable in the same trimester.
[f]Additional adjustment for the same exposure variable in the other trimester.
[g]Estimates are for each 10 ppb increase of NO_2.

the two entities a plausible explanation. Nonetheless, recognizing the potential for adjusting out some of the influence of spatial variation in air pollution by adjusting for hospital, the validity of the results with and without hospital adjustment is uncertain. The judgment about whether the study provides essentially null findings or a hint of adverse effects limited to gestational hypertension is open to varying interpretation. This potential source of confounding has not been considered in previous studies.[2]

Exposure misclassification is an important concern given that residential pollutant levels were estimated based on maternal residence at delivery. Women may have moved during the course of pregnancy, they spend time at locations other than their residence, and there is uncertainty in the levels estimated for a given location due to the modeling and variation resulting from height of the housing unit, open and closed windows, etc. Hospital discharge diagnoses have been found to be reasonably accurate in relation to full medical record reviews, but far from perfect. Positive predictive values for all hypertensive disorders are in the range of 85%–90%[26,33,34] and somewhat lower for all preeclampsia (54%–74%)[33,34] and gestational hypertension (56%),[34] but higher for severe preeclampsia (85%–100%).[34,35] The absolute prevalence of the disorders in our study—2.2% for gestational hypertension, 2.6% for mild preeclampsia, and 1.6% for severe preeclampsia—suggests an underreporting of gestational hypertension as might be expected for a more benign condition. That greater risk of underreporting allows for the possibility of variable underreporting by hospital, potentially affecting the pattern of association with air pollution. While there is the real possibility that misclassification of either the outcome or the exposure biased associations toward the null, relative to previous studies, ours has some methodologic strengths, lending credibility to our results.

Previous studies have reported positive associations between $PM_{2.5}$ and preeclampsia,[8,12,14] aggregated hypertensive disorders of pregnancy,[9,11] or mean blood pressure,[16] with absent or negligibly small associations found in other studies relating $PM_{2.5}$ to preeclampsia,[13,17] gestational hypertension,[13] or mean blood pressure.[15] The meta-analytic summary odds ratios for $PM_{2.5}$ in two recent meta-analyses were 1.6 and 1.2 per 5 $\mu g/m^3$ $PM_{2.5}$ for a constellation of hypertensive disorders of pregnancy and 1.3 and 1.1 for preeclampsia alone.[2,18] Given the large sample size of our study compared with prior studies, our estimated odds ratio for total hypertensive disorders with adjustment for hospital would likely move the meta-analytic summary estimate closer to the null.

Results for NO_2 and hypertensive disorders are similarly mixed although less abundant. Positive associations have been reported for preeclampsia,[8,20] and null or negligibly small associations for preeclampsia[12,14,19,21] and all hypertensive disorders.[11] Given prior meta-analytic results showing summary odds ratios of 1.4 and 1.1 per 10 ppb NO_2 for all hypertensive disorders, our results would again likely bring the meta-analytic summary estimate closer to the null.[2,18] It is difficult to discern a pattern among the studies that do and do not find positive associations, but the differences in effect estimates between "positive studies" (ORs ~ 1.2–1.4) and "negative studies" (ORs < 1.2) are rather modest and well within the range of random variation or subtle differences in exposure or outcome assessment or confounding.

It may be argued that we are quickly reaching the limits of benefiting from additional studies of a similar nature to those that have done before based on routinely available air pollution indicators and indicators of pregnancy complications. Whether the next one finds effect measures near the null or slightly elevated will have modest impact on the cumulative evidence for or against an association. Studies that can examine air pollution in relation to more refined measures of outcome using detailed clinical data that accounts for timing of onset or provide research-quality blood pressure measurements would bring a new perspective to the topic, regardless of whether associations are found. Methodologic insights into sources of confounding, such as the impact of delivery hospital, may also help to determine whether this effect needs to be considered in other studies of air pollution and pregnancy outcome.

REFERENCES

1. Shah PS, Balkhair T. Air pollution and birth outcomes: a systematic review. *Environ Int.* 2011;37:498–516.
2. Pedersen M, Stayner L, Slama R, et al. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. *Hypertension.* 2014;64:494–500.
3. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:391–403.
4. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation.* 2004;109:2655–2671.
5. Brook RD, Rajagopalan S, Pope CAIII, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation.* 2010;121:2331–2378.
6. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag*. 2011;7:467–474.
7. Ahn H, Park J, Gilman-Sachs A, Kwak-Kim J. Immunologic characteristics of preeclampsia, a comprehensive review. *Am J Reprod Immunol*. 2011;65:377–394.
8. Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. *Environ Health Perspect*. 2009;117:1773–1779.
9. Vinikoor-Imler LC, Gray SC, Edwards SE, Miranda ML. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. *Paediatr Perinat Epidemiol*. 2012;26:91–100.
10. Yorifuji T, Naruse H, Kashima S, et al. Residential proximity to major roads and preterm births. *Epidemiology.* 2011;22:74–80.
11. Xu X, Hu H, Ha S, Roth J. Ambient air pollution and hypertensive disorder of pregnancy. *J Epidemiol Community Health*. 2014;68:13–20.
12. Mobasher Z, Salam MT, Goodwin TM, Lurmann F, Ingles SA, Wilson ML. Associations between ambient air pollution and hypertensive disorders of pregnancy. *Environ Res*. 2013;123:9–16.
13. Lee PC, Roberts JM, Catov JM, Talbott EO, Ritz B. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. *Matern Child Health J*. 2013;17:545–555.

14. Dadvand P, Figueras F, Basagana X, et al. Ambient air pollution and preeclampsia: a spatiotemporal analysis. *Environ Health Perspect.* 2013;121:1365–1371.
15. Lee PC, Talbott EO, Roberts JM, et al. Ambient air pollution exposure and blood pressure changes during pregnancy. *Environ Res.* 2012;117:46–53.
16. Jedrychowski WA, Perera FP, Maugeri U, et al. Prohypertensive effect of gestational personal exposure to fine particulate matter. Prospective cohort study in non-smoking and non-obese pregnant women. *Cardiovasc Toxicol.* 2012;12:216–225.
17. Rudra CB, Williams MA, Sheppard L, Koenig JQ, Schiff MA. Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in western Washington State. *Environ Health Perspect*. 2011;119:886–892.
18. Hu H, Ha S, Roth J, Kearney G, Talbott EO, Xu X. Ambient air pollution and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Atmos Environ (1994)*. 2014;97:336–345.
19. Pereira G, Haggar F, Shand AW, Bower C, Cook A, Nassar N. Association between pre-eclampsia and locally derived traffic-related air pollution: a retrospective cohort study. *J Epidemiol Community Health*. 2013;67:147–152.
20. Malmqvist E, Jakobsson K, Tinnerberg H, Rignell-Hydbom A, Rylander L. Gestational diabetes and preeclampsia in association with air pollution at levels below current air quality guidelines. *Environ Health Perspect*. 2013;121:488–493.
21. 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.
22. van den Hooven EH, de Kluizenaar Y, Pierik FH, et al. Air pollution, blood pressure, and the risk of hypertensive complications during pregnancy: the generation R study. *Hypertension.* 2011;57:406–412.
23. Savitz DA, Bobb JF, Carr JL, et al. Ambient fine particulate matter, nitrogen dioxide, and term birth weight in New York, New York. *Am J Epidemiol.* 2014;179:457–466.
24. England L, Zhang J. Smoking and risk of preeclampsia: a systematic review. *Front Biosci*. 2007;12:2471–2483.
25. Strand LB, Barnett AG, Tong S. Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. *BMC Med Res Methodol*. 2011;11:49.
26. Lydon-Rochelle MT, Holt VL, Cardenas V, et al. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. *Am J Obstet Gynecol.* 2005;193:125–134.
27. Ross Z, Ito K, Johnson S, et al. Spatial and temporal estimation of air pollutants in New York City: exposure assignment for use in a birth outcomes study. *Environ Health.* 2013;12:51.
28. Clougherty JE, Kheirbek I, Eisl HM, et al. Intra-urban spatial variability in wintertime street-level concentrations of multiple combustion-related air pollutants: the New York City Community Air Survey (NYCCAS). *J Expo Sci Environ Epidemiol.* 2013;23:232–240.
29. Matte TD, Ross Z, Kheirbek I, et al. Monitoring intraurban spatial patterns of multiple combustion air pollutants in New York City: design and implementation. *J Expo Sci Environ Epidemiol.* 2013;23:223–231.
30. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health.* 2006;83:1041–1062.
31. Hajat A, Diez-Roux AV, Adar SD, et al. Air pollution and individual and neighborhood socioeconomic status: evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect.* 2013;121:1325–1333.
32. Shmool JLC, Kubzansky LD, Ito K, et al. Spatial correlations across community social stressors and outdoor air pollution in New York City: a GIS-based approach for social-environmental epidemiology. *Environmental Health.* 2014;13:91.
33. Yasmeen S, Romano PS, Schembri ME, Keyzer JM, Gilbert WM. Accuracy of obstetric diagnoses and procedures in hospital discharge data. *Am J Obstet Gynecol*. 2006;194:992–1001.
34. Klemmensen AK, Olsen SF, Osterdal ML, Tabor A. Validity of preeclampsia-related diagnoses recorded in a national hospital registry and in a postpartum interview of the women. *Am J Epidemiol*. 2007;166:117–124.
35. Geller SE, Ahmed S, Brown ML, Cox SM, Rosenberg D, Kilpatrick SJ. International Classification of Diseases-9th revision coding for preeclampsia: how accurate is it? *Am J Obstet Gynecol*. 2004;190:1629–1633; discussion 1633.