RESEARCH REPORT

HEALTH EFFECTS INSTITUTE

Number 189
September 2016

Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China

Zhengmin Qian, Bin Zhang, Shengwen Liang, Jing Wang, Shaoping Yang, Ke Hu, Edwin Trevathan, Rong Yang, Qijie Li, Louise H. Flick, Ronghua Hu, Zhen Huang, Yimin Zhang, Shixiang Hu, Jing Wang, Longjiao Shen, Yuan Lu, Hui Peng, Yuzhen Yu, Li Yang, Wei Chen, Wenjin Liu, and Wei Zhang

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with a Critique by the HEI Health Review Committee

Research Report 189

Health Effects Institute

Boston, Massachusetts

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Publishing history: This document was posted at *www.healtheffects.org* in September 2016.

Citation for document:

Qian Z, Zhang B, Liang S, Wang J, Yang S, Hu K, et al. 2016. Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China. Research Report 189. Boston, MA:Health Effects Institute.

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ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
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- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. This report by Z. Qian and colleagues was funded by the Public Health and Air Pollution in Asia (PAPA) program, initiated by HEI. Additional funding was obtained from the William and Flora Hewlett Foundation.

HEI has funded more than 330 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 1000 articles in the peer-reviewed literature.

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All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

ABOUT THIS REPORT

Research Report 189, *Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China,* presents a research project funded by the Health Effects Institute and conducted by Dr. Zhengmin Qian of St. Louis University College for Public Health and Social Justice, St. Louis, Missouri, and his colleagues. The report contains three main sections.

The HEI Statement, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Health Review Committee's comments on the study.

The Investigators' Report, prepared by Qian and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The Critique, prepared by members of the Health Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Health Review Committee, an independent panel of distinguished scientists who have no involvement in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Critique reflects the information provided in the final version of the report.

HEI STATEMENT

Synopsis of Research Report 189

Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China

BACKGROUND

Several recent studies have suggested that maternal exposures to air pollution and temperature extremes might contribute to low birth weight (LBW), preterm birth (PTB), and other outcomes that can adversely affect infant health. At the time the current study began, most other studies had been conducted in the United States or Europe. Dr. Zhengmin Qian proposed to extend work he had done on ambient particulate air pollution and daily mortality in Wuhan, China (Qian et al. 2010), as part of the HEI-sponsored Public Health and Air Pollution in Asia program, to study adverse birth outcomes. Wuhan is the capital city of Hubei province, has a large population of about 6.4 million within the urban study area, experiences temperature extremes, and generally has higher air pollution levels than those observed in the United States and Europe, thus providing a good opportunity to explore questions about air pollution and health.

APPROACH

Qian and colleagues planned a cohort and nested case–control design with four specific aims, examining whether increased exposures to air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO) during vulnerable pregnancy periods were associated with increased rates of PTB, LBW (<2500 g), or intrauterine growth retardation (IUGR, defined as having a birth weight below the 10th percentile of singleton live births in Wuhan) after adjusting for major risk factors and whether the associations were confounded by copollutant exposures, affected by residual confounding, or modified by temperature extremes, socioeconomic status (SES), or secondhand smoke (SHS) exposure.

The cohort study included 95,911 births that occurred from June 10, 2011, to June 9, 2013, and met typical prespecified inclusion criteria used in other birth outcome studies. The case–control study included 3146 cases (PTB, LBW, or both, but not IUGR) and 4263 controls (matched to the cases by birth month) for whom investigators were able to complete home visits and questionnaires.

The investigators obtained air pollution and daily weather data for August 2010 to June 2013 from nine monitoring stations representing background air pollution sites in seven Wuhan inner-city districts. Only two of these stations provided $PM_{2.5}$ data. For the

What This Study Adds

- The investigators created one of the largest administrative cohorts in a major Chinese city with which to examine their hypotheses about the effects of exposures to $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 and other key covariates on preterm birth, low birth weight, and intrauterine growth retardation.
- In cohort and case–control studies, the investigators found weak evidence of effects of exposure to air pollution during the entire pregnancy on preterm birth and low birth weight. The effects were similar, in some cases, to those found in other studies. They found limited evidence of air pollution effects on intrauterine growth retardation and found analyses of vulnerable exposure windows to be inconclusive.
- In the HEI Review Committee's view, given a number of challenges, including unresolved differences between the findings of the cohort and case–control studies, the results should be considered suggestive rather than conclusive, and should be interpreted carefully together.
- Given the opportunities created by this data set, the Committee encourages further exploration and analysis by the investigators going forward.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Zhengmin Qian at Saint Louis University College for Public Health and Social Justice, St. Louis, Missouri, and colleagues. Research Report 189 contains both the detailed Investigators' Report and a Critique of the study prepared by the Institute's Health Review Committee.

cohort study, the investigators assigned exposures to mothers according to the daily mean concentrations from the monitor nearest the residential community in which the mother lived at the time of the birth. For the case–control study, they assigned exposures based on the inverse distance weighted average of daily mean concentrations from the three nearest monitors, for all but $PM_{2.5}$ for which the method was not specified.

They also collected data on various factors that might confound or modify the impact of the pollutants on the adverse outcomes, including data collected in the cohort from mothers at the time of delivery and, in the case–control study, from questionnaires administered to mothers. In the case–control study, covariates representing SES (as indicated by the mother's educational attainment and household income) and SHS exposures were of particular interest.

The primary statistical analyses of the pollutant associations with PTB, LBW, and IUGR were conducted using logistic regression models. In the cohort study, exposures during the pregnancy period of interest (full term, trimesters, and selected months) were included as continuous variables. In the case–control study, the exposures were modeled as binary variables (i.e., above or below the median pollutant concentrations). Numerous sensitivity analyses were conducted.

RESULTS AND INTERPRETATION

Although originally planning a nested case–control study, the investigators encountered challenges that led them to analyze the cohort and case–control studies using different ways of assigning exposures and characterizing them in their statistical models. These decisions precluded direct comparisons between the sets of results, making it difficult to answer the questions about residual confounding that nested case–control studies are designed to answer. The odds ratios from the two study designs using different exposures also have different interpretations.

Still, one can ask whether the sets of findings were qualitatively consistent with each other or with those of similar studies. There were some similarities. Both studies suggested that increased $PM_{2.5}$, PM_{10}, CO, and O_3 exposures over the full pregnancy were associated with small increases in the odds of PTB (the case–control study also showed an association with NO_2) and that increased $PM_{2.5}$ exposures were associated with significantly increased odds of LBW. However, most of the other pollutants had no effect on LBW, except CO in the cohort study and O_3 in the case–control study, both of which increased the odds of LBW. The exposures over the entire pregnancy were generally associated with decreased odds of IUGR. Adjustments for potential confounders were greatest for the delivery covariates.

The investigators found no systematic association of any of these outcomes with particular trimesters or months, another result that differed from those of some other studies. They found little evidence that their main results were confounded or modified by the presence of copollutants, although with the exception of O_3, most of the pollutants were highly correlated, making it difficult to disentangle the effects of individual pollutants.

Could the two sets of data be analyzed in a more comparable way, as in a standard nested case–control study? At the Committee's request, the investigators reanalyzed the case–control data using the same exposures and models as in the cohort study. The results were strikingly different from those using the inverse distance weighted exposures, modeled as binary variables — the pollutants had either no effect or an apparent beneficial effect on PTB and LBW. The Committee was not convinced by the explanations offered for these differences, leaving the reasons for them unresolved.

CONCLUSIONS

This study set out to answer important questions about the effects of air pollution exposure on three measures of adverse birth outcomes — LBW, PTB, and IUGR — in a large cohort of mothers and newborns in Wuhan, China. Given the cohort size, high pollution levels and temperatures, and detailed covariate data, the investigators were well poised to address these questions. They sought to pattern their work on other studies of birth outcomes, were very responsive to Committee questions, and provided many additional analyses and explanations.

In the Committee's view, however, the study was unable to address with confidence several of its specific aims. Most important, the differences in results when the case–control data were analyzed with different exposure metrics remain unexplained, raising concerns about the ability to draw conclusions from subsequent analyses assessing residual confounding and effect modification by temperature extremes, SES, and SHS exposure. Consequently, any individual findings from the cohort and case–control studies should be considered suggestive rather than conclusive, and should be interpreted carefully together.

INVESTIGATORS' REPORT

Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China

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ABSTRACT

Studies in Western countries have suggested that ambient air pollution is positively associated with adverse pregnancy outcomes, but the levels of pollutant exposures assessed in these studies have been relatively low, limiting confidence in the studies' conclusions. In Asia, where exposure levels have been higher, there have only been a limited number of studies of associations between air pollution and adverse pregnancy outcomes. Two methodological challenges have been identified in the existing studies: confounding and effect modification and the need to identify vulnerable windows of exposure during pregnancy. The current population-based prospective cohort study and nested case–control study was designed to investigate the associations between air pollution and adverse pregnancy outcomes in Wuhan, China, and to address the limitations of some of the earlier studies. Our primary objective was to evaluate whether high levels of pollution, including particulate matter (PM**) ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$), PM ≤10 μm in aerodynamic diameter (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), or carbon monoxide (CO) are associated with increased occurrences of preterm birth (PTB), low birth weight (LBW), or intrauterine growth retardation (IUGR) in a cohort of 95,911 live births during a 2-year period from June 10, 2011, to June 9, 2013. Our four primary aims were to examine (1) the effects of ambient concentrations of pollutants during vulnerable pregnancy periods on adverse pregnancy outcomes, adjusted for major risk factors; (2) whether the associations were confounded by copollutants; (3) how much residual confounding affected the associations; and (4) whether the associations were modified by temperature extremes (high or low), socioeconomic status (SES), or secondhand smoke (SHS) exposure.

We collected data on daily mean concentrations of pollutants from nine air monitoring stations operated by the Wuhan Environmental Monitoring Center (WEMC) in seven urban core districts in Wuhan. Data on PTB, LBW, and IUGR during the study period were collected through the comprehensive perinatal health care system of the Wuhan Medical and Health Center for Women and Children.

To address the first aim, we used logistic regressions to characterize the relationships between exposure to each of the pollutants during various pregnancy periods and adverse pregnancy outcomes while controlling for important covariates. The dichotomous dependent variables included PTB, LBW, and IUGR. The exposure variables

This Investigators' Report is one part of Health Effects Institute Research Report 189, which also includes a Critique by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr. Zhengmin (Min) Qian, Department of Epidemiology, College for Public Health and Social Justice, Saint Louis University, Salus Center/Room 473, 3545 Lafayette Avenue, Saint Louis, MO 63104; e-mail: *zqian2@slu.edu*.

This study by Qian and colleagues was conducted as part of the Public Health and Air Pollution in Asia (PAPA) program, initiated by HEI. Additional funding was obtained from the William and Flora Hewlett Foundation. The contents of this document have not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* Co-principal investigators.

** A list of abbreviations and other terms appears at the end of the Investigators' Report.

were daily mean concentrations of pollutants estimated using the pollutants' measurements from the closest monitors. Effect estimates were derived based on unit increases specific to the pollutants: 5 μg/m^3 for PM_{10} and $PM_{2.5}$, 3 μg/m^3 for SO_2 and NO_2, 10 μg/m^3 for O_3, and 100 μg/m^3 for CO.

To address the second aim, we conducted analyses with two-pollutant models to test possible confounding effects among pollutants. The same models described for the first aim were fitted first, and the copollutants were then included one by one.

To address the third aim, we performed logistic regressions while controlling for additional covariates collected from a questionnaire in the nested case–control study. Cases were defined as all PTBs and all LBW births and, as controls, a comparable number of randomly sampled normal births (full term and normal weight). Cases and controls were matched by birth month.

To address the fourth aim, we addressed possible effect modifications by several factors on the associations between the various pollutant concentrations and birth outcomes. Potential effect modifiers included temperature extremes, maternal educational attainment, household income, and SHS exposure.

We found small but consistently positive associations between $PM_{2.5}$, PM_{10}, CO, and O_3 concentrations across the entire pregnancy and both PTB and LBW. For PTB, for each 5-μg/m^3 increase in $PM_{2.5}$ and PM_{10} concentrations, 100-μg/m^3 increase in CO concentrations, and 10-μg/m^3 increase in O_3 concentrations, we observed odds ratios (ORs) of 1.03 (95% CI, 1.02–1.05); 1.02 (95% CI, 1.02–1.03); 1.15 (95% CI, 1.11–1.19); and 1.05 (95% CI, 1.02–1.07), respectively. We also observed negative associations for SO_2 or NO_2 and the ORs for both PTB and LBW; the ORs were close to the null, and some of them were not statistically significant. The majority of the estimated effects from two-pollutant models were similar to those estimated from single-pollutant models. The observed associations, while controlling for the covariates collected at the delivery, appeared not to be biased by residual confounding. No critical exposure windows were identified consistently. The largest effects for PTB, for example, were found in the second trimester for $PM_{2.5}$, PM_{10}, and CO, but for SO_2 the largest effects were in the first trimester, second month, and third month. For NO_2 they were in the first trimester and second month, and for O_3, the third trimester. We also examined temperature extremes, maternal educational attainment, household income, and SHS exposure as effect modifiers. No clear patterns were observed for the modification of temperature extremes, and larger effects were observed for both low and high temperature days. The largest effect of $PM_{2.5}$ on PTB, for example, was on high temperature days. For maternal educational attainment, we did not observe any statistically significant interactions for PTB. In general, women with lower attainment had higher rates of LBW associated with $PM_{2.5}$, PM_{10}, and CO exposure than those with higher attainment. No clear interaction patterns were observed for SO_2, NO_2, and O_3. We observed no consistent interaction pattern for IUGR for any pollutant. For household income, we observed some statistically significant interactions for PTB and LBW but found no consistent pattern of interactions.

In conclusion, our findings show associations between air pollutants and adverse pregnancy outcomes. The results from the case–control study in general support those from the cohort study for the majority of the observed associations for PTB and LBW. In addition, few previous studies have examined effect modification of these associations by temperature extremes, maternal educational attainment, household income, or SHS exposure. However, we need more toxicological studies and prospective cohort studies with better exposure assessments to assess causality related to specific pollutants.

INTRODUCTION

In recent years, an increasing number of air pollution exposure studies have explored effects on less traditional health endpoints, including cardiovascular system effects (Levinsson et al. 2014) and adverse pregnancy outcomes (Basu et al. 2014; Ebisu and Bell 2012; Faiz et al. 2012; Ha et al. 2001; Hansen et al. 2008; Jiang et al. 2007; Ross et al. 2013; Savitz et al. 2014). A growing body of evidence has suggested that exposure to air pollution may increase the risk of PTB, LBW, and IUGR (Ezziane 2013; Gray et al. 2014; Huynh et al. 2006; Liu et al. 2003; Padula et al. 2012; Pereira et al. 2014; Ritz et al. 2000; Sagiv et al. 2005; Yorifuji et al. 2013;). PTB (delivery before 37 completed weeks of gestation) and LBW (<2500 g) are the most important predictors of neonatal mortality (death in the first 28 days) and infant mortality (death in the first year) in both developed and developing countries (Behrman and Butler 2007; Blencowe et al. 2012; Institute of Medicine 2009; National Institutes of Health 2013; World Health Organization 2004).

In the developing world, about 15.5% of overall births (more than 20 million) per year are LBW infants (Goldenberg et al. 2008). Worldwide, 9.6% of overall births (12.9 million) per year are preterm, and approximately 85% of them occur in Asia and Africa (Beck et al. 2010). Babies born preterm, LBW, or with IUGR are at an increased risk

for both short- and long-term health effects (Chernausek 2012; Stoll et al. 2004; Verrips et al. 2012). PTB and LBW infants are at increased risk of neurodevelopmental impairment and respiratory and gastrointestinal complications (Baraldi and Filippone 2007; Bhutta et al. 2002; Marlow et al. 2005). Preterm, LBW, or IUGR births are also associated with the development of type 2 diabetes, hypertension, and cardiovascular disease in adulthood (Saigal and Doyle 2008). It is not clear why the PTB rate is so high; the causation appears to be complex and is poorly understood (Institute of Medicine 2009; Perera et al. 2003, 2004), but interrelated biological, physical, psychological, and social factors are thought to play a significant role (Institute of Medicine 2009; National Institutes of Health 2013).

An increasing number of studies have examined the effects of air pollution on adverse pregnancy outcomes, including studies in China (Hwang et al. 2011; Jiang et al. 2007; Xu et al. 1995; Zhao et al. 2011), South Korea (Lee et al. 2002; Seo et al. 2010), Japan (Kashima et al. 2011), the United States (Bell et al. 2007; Chang et al. 2012; Ghosh et al. 2013; Gray et al. 2010, 2013, 2014; Iñiguez et al. 2012; Kloog et al. 2012; Laurent et al. 2013; Morello-Frosch et al. 2010; Parker et al. 2005; Ritz and Yu 1999; Ritz et al. 2002, 2007; Sagiv et al. 2005; Salam et al. 2005; Vinikoor-Imler et al. 2014; Wilhelm et al. 2012; Wu et al. 2009; 2013; Xu et al. 2011), Canada (Brauer et al. 2008; Liu et al. 2003), England (Dolk et al. 2010; Pearce et al. 2010; Rankin et al. 2009), the Netherlands (Gehring et al. 2011a), Spain (Ballester et al. 2010; Llop et al. 2010), Sweden (Landgren 1996), Norway (Madsen et al. 2010), Poland (Edwards et al. 2010), Italy (Schifano et al. 2013), Brazil (Gouveia et al. 2004; Nascimento and Moreira 2009; Pereira et al. 1998), Australia (Hansen et al. 2007, 2008), and the Czech Republic (Bobak 2000; Dejmek et al. 2000). Despite the fact that most published studies have reported that various air pollutants are associated with PTB and LBW, variability exists in the nature of the studied pollutants and associated pregnancy outcomes (Darrow et al. 2009; Dejmek et al. 2000; Rich et al. 2009; Salam 2008; Wilhelm and Ritz 2005). Heterogeneous associations, including negative associations and effects of small magnitude, have also been observed. It is a challenge to synthesize these findings because of the differences in exposure scenarios, study populations, study designs, and analyses (Bosetti et al. 2010; Dadvand et al. 2013, 2014; Maisonet et al. 2004; Polichetti et al. 2013; Ritz and Wilhelm 2008; Stieb et al. 2012; Stillerman et al. 2008; Warren et al. 2013; Woodruff 2013; Woodruff et al. 2009).

The mechanisms by which air pollution affects pregnancy outcomes are not entirely clear but may be similar to those by which SHS exposure in pregnancy has been shown to affect offspring (Andres and Day 2000; Kannan et al. 2006; Wang and Pinkerton 2007). The hypothesized mechanisms include disturbance of uterine blood flow, disturbance of the pituitary-adrenocortical system (which in turn affects the placenta), or the immune system, causing increased maternal susceptibility to infections (Manzo et al. 2012; Oberdörster and Utell 2002; Vadillo-Ortega et al. 2014), disruption of Treg function and of T-cell regulation and differentiation during the fetal period (Kannan et al. 2006; Mold et al. 2008; Nold et al. 2012; Saito et al. 2007), oxidative stresses and local and systemic inflammation (Angiolini et al. 2006; Kannan et al. 2006; Risom et al. 2005; Slama et al. 2008a), epigenetic modulations (Baccarelli et al. 2009; Galazka et al. 2009), and an influence over the expression of specific maternal and fetal genotypes (Adams and Eschenbach 2004; Engel et al. 2005).

It has also been hypothesized that studies of air pollution effects on pregnancy have been plagued by residual confounding from unmeasured demographic factors and risk factors (Ha et al. 2014; Lacasana et al. 2005; Lee et al. 2002, 2008; Liu et al. 2007; Nieuwenhuijsen et al. 2013; Savitz et al. 2014; Woodruff et al. 2003). Thus, air pollution and pregnancy-outcome studies to date have been hampered by at least two methodological challenges: confounding and effect modification and the need to identify vulnerable windows of exposure during pregnancy (temporality of effects).

CONFOUNDING AND EFFECT MODIFICATION

Environmental epidemiological studies are observational. As such, they are open to confounding (Ghosh et al. 2007; Rothman et al. 2008). Adverse pregnancy outcomes attributed to air pollution are not specific and may also be attributable to other factors, including SES, indoor pollution sources, social stressors, and influences from other comorbidities. People of lower SES, for example, are more highly exposed to pollution, because they move where housing prices are lowest, they have less power to prevent exposure, they have less access to environmental health information, or certain aspects of their lifestyle are associated with greater deprivation (Genereux et al. 2008; Ponce et al. 2005; Slama et al. 2007). While there are well-documented differences in the risk of poor pregnancy outcomes across demographic and ethnic groups, it is not clear to what extent socio-demographic factors, indoor pollution sources, behavioral factors, and other factors interact with air pollutants or how they may increase exposure to pollution from various sources and increase the risk of poor pregnancy outcomes (Triche and Hossain 2007). Many studies have only incorporated a limited number of these factors because they relied on birth certificate data, and

important covariates — such as indoor pollution sources, behavioral factors, psychosocial factors, and maternal health history — were not available.

Thanks to extensive data collection, including high-quality data collected at birth (i.e., the delivery dataset) and detailed questionnaire data (e.g., total household income, SHS exposure, maternal chronic medical conditions, and living close to a main road, as well as depression, negative events, weight gain, moving, and vaginal bleeding during pregnancy), the current study was able to address critical questions about residual confounding and effect modification.

VULNERABLE WINDOWS OF EXPOSURE

There has been a lack of toxicological data to provide guidance in selecting the most vulnerable exposure windows during pregnancy (Gilboa et al. 2005; Glinianaia et al. 2004). Previous investigations used a broad range of exposure windows (i.e., weeks, months, or trimesters) to explore the temporal relationships between air pollution and adverse pregnancy outcomes (Dugandzic et al. 2006; Gouveia et al. 2004; Hansen et al. 2007; Mannes et al. 2005; Medeiros and Gouveia 2005; Parker et al. 2005; Salam et al. 2005; Slama et al. 2006; Wilhelm and Ritz 2003). Some studies reported that exposure during the first trimester was associated with an increased risk of PTB or LBW (Bobak 2000). Other studies have suggested that third-trimester exposures had greater effects (Maisonet et al. 2001; Ritz and Yu 1999; Wang et al. 1997). We still do not know whether the peak effect period differs across populations and pollutants (Selevan et al. 2000; Slama et al. 2008b). Thus, it has not yet been possible to synthesize the findings on the temporality of exposures to specific pollutants or determine which pollutants contribute most to PTB or LBW (Woodruff et al. 2009).

With detailed estimated exposure metrics, the current study was able to explore critical exposure windows and metrics that influence the adverse pregnancy outcomes for each pollutant.

The study was designed to address the aformentioned gaps by testing the research hypotheses that addressed (1) the independent health effects of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO on PTB, LBW, and IUGR during a range of pregnancy periods; (2) the extent to which residual confounding may affect the estimated associations by controlling for covariates recorded in delivery and questionnaire datasets; and (3) identification of subgroups that might be particularly susceptible to air pollution because of extremes of temperature, SES (maternal education attainment and household income), and SHS.

SPECIFIC AIMS

The primary objective was to evaluate whether high pollution levels of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO are related to increased occurrence of PTB, LBW, and IUGR in a cohort of 95,911 neonates born in Wuhan, China, during a 2-year period from June 10, 2011, to June 9, 2013. Our specific aims were to test four hypotheses:

1. That elevated ambient concentrations during vulnerable pregnancy periods are associated with increased adverse pregnancy outcomes when adjusting for major risk factors.
2. That these associations are confounded by copollutants.
3. That residual confounding affects the associations.
4. That the associations are modified by extremes of temperature, SES, household income, or SHS exposure.

We followed a cohort of 95,911 mothers-to-be in the seven inner-city districts of Wuhan. Delivery data were obtained from the Wuhan Medical and Health Center for Women and Children's electronic database. For the majority of the mothers-to-be, data about the first prenatal care visit were also obtained from the Center. We selected a case–control sample of 3145 cases and 4264 controls from within the cohort. To enhance our ability to assess the extent to which residual confounding might affect the associations, we collected additional detailed information from both the cases and the controls by interview, including family income, indoor pollution sources, parental smoking, alcohol consumption, time activity pattern, distance between the residence and major roads, and distance between the residence and the closest air pollution monitors. We collected daily mean $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO concentrations from nine monitoring stations (only two for $PM_{2.5}$) (Figure 1) operated by the Wuhan Environmental Monitoring Center (WEMC). Daily temperature and humidity data were also collected by the WEMC. Finally, we used multiple logistic regression models to test our research hypotheses.

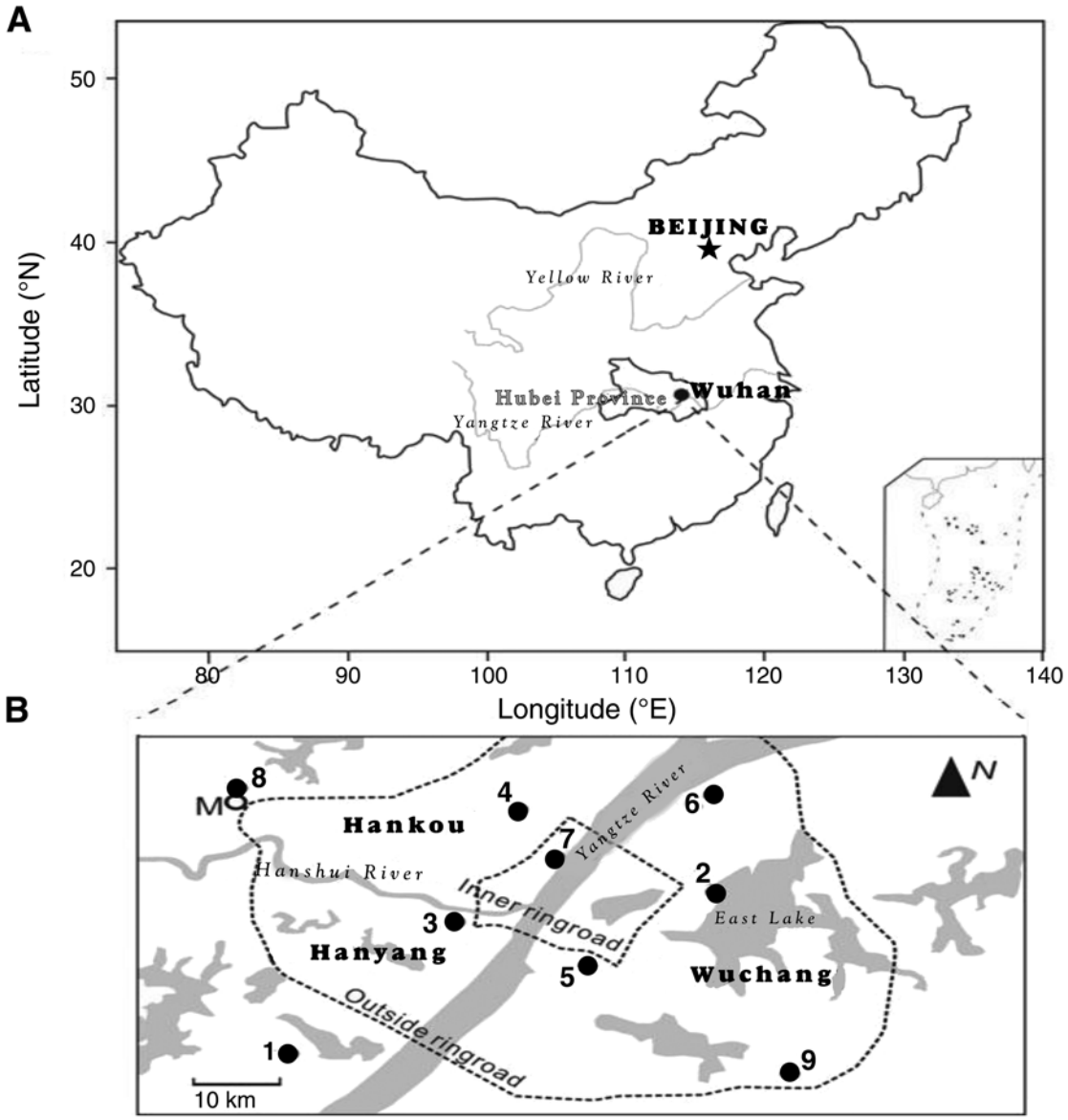

Figure 1. The black dots represent the locations of Wuhan's nine ambient air monitoring stations. Note that $PM_{2.5}$ was measured only at stations 2 and 8. (From Feng et al. 2011. Used with permission of Springer Science+Business Media.)

METHODS AND STUDY DESIGN

STUDY DESIGN

We used an efficient, cost-effective study design to assess pollution-related effects in this study. The research was conducted in two phases.

Phase I involved a prospective population-based cohort study to address specific aims 1 and 2. In this phase, we followed the 95,911 pregnant women living in the seven inner-city districts in Wuhan during the 2-year study period. All pregnant women living in the targeted districts of Wuhan received their prenatal care from, and delivered through, the Wuhan Medical and Health Center for Women and Children. The Center used a single integrated information system; we collected from this electronic record data on the first prenatal care visit, delivery, and postnatal period for each woman. Data from the WEMC included daily mean concentrations of ambient $PM_{2.5}$, PM_{10}, SO_2,

NO_2, O_3, and CO. We examined associations between PTB, LBW, and IUGR and estimated exposures throughout a broad range of exposure windows during pregnancy.

Phase II involved a case–control study addressing specific aim 3. We selected a case–control sample of 7409 births nested in the birth cohort. The cases were defined as either a PTB (<37 completed weeks gestation) or LBW (<2500 g) (Ritz et al. 2007); all preterm and LBW births were included. A comparable number of controls (≥37 completed weeks gestation and ≥2500 g weight) were randomly selected from the same inner-city districts. Cases and controls were selected three times per month, on the 10th, 20th, and last day of each month. Births from the 1st to the 10th day of the month were sampled on the 20th day of the month. Births from the 11th to 20th days were sampled on the last day of the month. Births from the 21st day to the last day were sampled on the 10th day of the following month. This schedule ensured that subsequent interviews were completed within a range of 42 days to 3 months of delivery and that all births were included in the sampling frame in a timely fashion. We were not particularly concerned about the overmatch of this recruiting method, because the sample denominators of each sampling period (i.e., the total *N* of cases and the total *N* of potential controls) were available by the end of each sampling period, and we used sampling weights in our subsequent two-phase data analyses (Appendix L, available on the HEI Web site) (Hoggatt et al. 2009). We visited the homes of each case and control, collected additional data on household income, indoor pollution sources (e.g., passive smoking), occupational exposures, smoking, alcohol consumption, the addition of folic acid, maternal disease history, pregnancy complications, maternal time–activity patterns, distance between residence and major roads, and distance between residence and the closest monitor. These additional data were used to assess the extent to which residual confounding might have been affecting the associations. The Institutional Review Board of Saint Louis University approved the study protocol.

STUDY PERIOD AND STUDY AREA

Wuhan, the capital of Hubei Province, is the largest city in Central China and is located in the middle of the Yangtse River delta, at 29°58′–31°22′ N, 113°41′–115°05′E. It has a population of approximately 10 million people, of whom approximately 6.4 million live in seven urban core districts. Wuhan occupies a land area of 8494 km^2 and has a humid subtropical monsoon climate, with hot, humid summers. Its average daily maximum temperature in July is 37.2°C, and the maximum daily temperature often exceeds 40°C. Because of its hot summers, Wuhan has been called an "oven" city in China. The lowest daily average temperature in January is lower than 1.0°C.

The principal industrial activities of Wuhan include ferrous smelters and chemical, power, and machinery plants. Wuhan is one of the biggest hubs for land, water, and air transportation in China. The principal sources of air pollution in the city are motor vehicles and the use of coal for industrial processes. With high concentrations of pollutants and a relatively stable population, Wuhan provides a unique opportunity to examine the effects of air pollution on adverse pregnancy outcomes (Qian et al. 2001).

DATA COLLECTION

We collected our data from three sources (Appendix A, available on the HEI Web site). Delivery data for the cohort were obtained from the comprehensive perinatal health care system of the Wuhan Medical and Health Center for Women and Children. Questionnaire data for the nested case–control study came from interviewing participants during home visits. Daily weather and air pollution data were collected by nine monitoring stations (only two for $PM_{2.5}$) of the Wuhan Air Automatic Monitoring System, which is operated by the WEMC.

AIR POLLUTION AND WEATHER DATA

Air pollution data were collected by the WEMC. These data were used in the HEI-sponsored PAPA Time-Series Studies in Wuhan (Qian et al. 2007b,c, 2008) as well as in the U.S. Environmental Protection Agency (EPA)–sponsored Chinese Four Cities Study (Qian et al. 2000; 2007a). We used daily mean concentration data for $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO from the nine monitoring stations (only two of these monitoring stations collected measurements of $PM_{2.5}$) of the Wuhan Air Automatic Monitoring System for the period from August 19, 2010, to June 9, 2013 (Figure 1). The WEMC established the stations to measure background pollution levels for the whole city. There were no significant local pollution sources close to any of the stations. The median (minimum–maximum) distance between a monitoring station and the center of the community where participants lived was 3.1 km (0.1 km–9.7 km) for PM_{10}, SO_2, NO_2, O_3, and CO and 4.6 km (0.1 km–17.3 km) for $PM_{2.5}$. Each of the seven urban core districts included multiple communities in Wuhan. The measurements were collected automatically and continuously, 24 hours a day, 365 days a year, without interruption. The $PM_{2.5}$ measurements were made using beta attenuation monitors (BAM-1020, Met One Instruments, Grants Pass,

OR) (Appendices A and B). PM_{10} was collected using a tapered element and oscillating microbalance (RP1400a and RP1405d, Thermo Fisher Scientific, Waltham, MA, USA). SO_2 measurements were made using ultraviolet fluorescence (100e, Teledyne API, San Diego, CA, USA; 43i, Thermo Fisher Scientific). NO_2 measurements were made using chemiluminescence detection (200e, Teledyne API; 42i, Thermo Fisher Scientific). For the CO measurements, we used gas filter correlation (300e, Teledyne API; 48i, Thermo Fisher Scientific). The O_3 measurements were made using ultraviolet photometry (400e, Teledyne API; 49i, Thermo Fisher Scientific). The quality assurance and quality control procedures mandated by China's State Environmental Protection Administration (2012) for taking such measurements were strictly followed. Details of these procedures are included in Appendix G. Briefly, the WEMC conducted regular quarterly performance audits and precision checks on the air monitoring equipment and regular quarterly performance audits to assess data accuracy on all monitoring systems. Meteorological data, including temperature and relative humidity, were collected from each air monitoring station.

We estimated exposure using two approaches: a nearest-monitor approach for the cohort study and an inverse-distance-weighting approach for the nested case–control study. Details of the approaches are presented in Appendix C and Appendix D. For the nearest-monitor approach, we estimated exposures based on the mother's residential community at the birth of the index child. For each day, we assigned a daily mean pollutant concentration measured from the monitor closest to the community of interest. All mothers in a community were assigned the same daily mean concentrations. Eligible mothers had to live in a community that was wholly or partially within 5 km (15 km for $PM_{2.5}$) of a monitoring station, a distance that is shorter than those used in the majority of previous studies (Le et al. 2012; Wilhelm and Ritz 2005). For the inverse-distance-weighting approach, we estimated exposures based on home addresses at birth, using an inverse distance (1/distance) weighted average of the three closest monitors within 5 km of the mothers' home to compute a daily mean concentration for each mother.

Using the estimated date of conception as 14 days after the first day of the last menstrual period (LMP), we constructed three levels of surrogates for pollutant exposures for various time windows during pregnancy: (1) the mean level of exposure from the first day of pregnancy to delivery, which allowed assessment of exposure during the entire pregnancy and for 7 to 14 days before conception; (2) the mean level of exposure for the first trimester (first 91 days), second trimester (second 91 days), and third trimester (all remaining days) of the pregnancy, which allowed assessment of the exposure level during the various gestational stages; and (3) the mean level of exposure for the first month (first 30 days), second month (second 30 days), third month (third 30 days), next-to-last month (31 to 60 days before the delivery date), and last month (last 30 days before the delivery date) of pregnancy, which allowed assessment of the exposure level during various months. Similar definitions have been applied in previously published studies (Bell et al. 2007; Parker et al. 2005; Rich et al. 2009). These surrogates of exposure were chosen to provide the most relevant comparisons possible with previous studies (Liu et al. 2003; Parker et al. 2008; Ritz et al. 2007).

PREGNANCY OUTCOME AND COVARIATE DATA

Regulatory policy in Wuhan requires that the Wuhan Medical and Health Center for Women and Children electronically archives all delivery and first-prenatal-care-visit information. To improve perinatal outcomes, the Center established a regional comprehensive perinatal health care system two decades ago. The system consists of maternal–infant health care centers at three levels: city, district, and community. One of the major purposes of the system is to allow surveillance of adverse pregnancy outcomes. All pregnant women are required to register at their district's maternal health care center within 3 months of becoming pregnant. During their first prenatal care visit, pregnant women receive a manual with instructions for prenatal and postnatal care as well as forms for obstetricians to record data on maternal age, height, weight, education, occupation, date of the first day of their LMP, number of prenatal visits, medical history, date of delivery, infant sex, birth weight, and gestational age. They also receive a complete physical examination, including an ultrasound examination. After delivery, mothers are required to visit the community maternal health care centers for follow-up care, where the health care workers arrange a series of postnatal visits based on the information reported on the returned manual. In addition, the perinatal health care system requires that health care workers at the community maternal–infant health care centers visit a woman at her home within 42 days of her delivery. The regionalized perinatal health care system in Wuhan and the requirement to start care early make it possible to collect data on women from early pregnancy to delivery — which is why it was feasible for us to complete the large number of home interviews (7409 cases and controls) in our study. Because of China's "one child" policy, the majority of women were having their first planned pregnancy.

The Wuhan Medical and Health Center for Women and Children was one of the first three centers in China to standardize its women's and children's health information system. Because of its excellent infrastructure and performance, the Wuhan electronic data system is the only one approved by the National Center for Women's and Children's Health of the Chinese Center for Disease Control and Prevention. Strict, standardized quality assurance and control procedures are applied in the system (Appendix E, available on the HEI Web site). Briefly, delivery data is validated four times per year. Computerized data is examined against the original records at delivery hospitals. Each new live-born infant must be registered at a community maternal–infant health care center. Information on delivery is updated every month, including confirmation of the newborn infants' name, sex, date and time of birth, and parental names. Four to five randomly selected community maternal–infant health care centers are chosen for data audits in each of the seven districts every year. Birth certificates are not allowed to have missing data. Statistics on live-born delivery, PTB, and LBW are collected every 3 months. The Wuhan Medical and Health Center for Women and Children is responsible for training the district centers' health care workers, who are then responsible in turn for training the community centers' health care workers who collect the data.

Our outcomes definitions were developed in accordance with the World Health Organization's definitions. PTB is defined as a live birth before 37 completed weeks of gestation. LBW is defined as a live-born infant weighing less than 2500 g. IUGR is defined as an infant whose birth weight falls below the 10th percentile of all singleton live births in Wuhan, born between 2011 and 2013, who was in the same stratum by sex and week of gestation as the target IUGR infant. Historically, there has been a relatively low prevalence of adverse pregnancy outcomes in Wuhan compared with those of the United States (e.g., only 4.5% of births in the study population were PTB compared with 12.5% in the United States).

Covariate Data

PTB or LBW — which are associated with multiple risk factors — are among the most widely recognized yet least understood phenomena in the study of reproductive health. To enhance our ability to control potential confounding and to assess potential effect modifiers, we collected a wide range of information.

Covariates collected at the delivery included maternal age, ethnicity, parity, education, occupation, home address, date of the first day of the LMP, infant sex, year of birth, season of conception (calculated from the date of the first day of LMP), and temperature at conception (average daily temperature for 1 week with the estimated conception date in the middle). Covariates collected by interview using the questionnaire included family income, SES, education levels of both parents, weight gain during pregnancy, and residential history. The questionnaire also asked for data on covariates involving housing characteristics, including house type, location of the house (i.e., whether it directly faced a major road), opening of windows, and use of air conditioning. Information about sources of indoor pollution were also collected, including exposure to SHS and personal cigarette smoking, fuels used for cooking and heating, pets, pests, and home dampness. Behavioral and occupational exposure covariates assessed from the survey included nutrition (dietary composition and fish and fish oil consumption), sexual activity, physical activity, cigarette smoking, alcohol consumption, pharmaceutical use history, and use of personal care products. Psychosocial factors assessed included stress (life events and chronic and catastrophic stress), emotional responses and affective states (anxiety and depression), social support, and personal resources. Lastly, maternal health history was assessed, including asthma, infections, systemic lupus erythematosus, restrictive lung disease, hyper- or hypothyroidism, cardiac disease, gestational diabetes, hypertensive disorders of pregnancy, and preeclampsia.

Home Visits

A questionnaire completed by the mothers during the interviews was developed in both English and Chinese (Appendix F). The full and final version of the questionnaire included input and modifications from local investigators according to the environment in the study city. Written informed consent was obtained, and the questionnaires were completed during home visits within 3 months of delivery. All interviewers were appropriately trained and certified before the surveys.

Data management is presented in Appendix G, with database structure and codebooks for delivery data (Appendix H), first prenatal care visit data (Appendix I), and questionnaire data (Appendix J).

STATISTICAL METHODS AND DATA ANALYSIS

GENERAL ANALYTIC STRATEGIES AND REPORTING

The fundamental hypothesis of our study was that variations in air pollutant levels are associated with variations in adverse pregnancy outcomes (Greenland 1989). We

were interested in analyzing three outcomes: PTB, LBW, and IUGR. These outcomes, defined as dichotomous categories, were the dependent variables in our analysis. Daily mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO were the independent variables. To examine the relative importance of timing and magnitude of pollutant exposure in relation to adverse pregnancy outcomes, we constructed three levels of exposure surrogates for the studied pollutants: (1) the mean level of exposure from the first day of the LMP to delivery, which allowed assessment of exposure during the entire pregnancy; (2) the mean level of exposure for the first, second, and third trimesters, which allowed assessment of the exposure level during the various gestational stages; and (3) the mean level of exposure for the first, second, third, next-to-last, and last months of pregnancy, which allowed assessment of the exposure level during various months. The surrogates were developed by linking the pollution data with the pregnancy outcome data. Dates of the air pollution records were matched to the date of birth and date of the first day of the LMP to cover the gestation length. We then averaged the hourly measurements arithmetically for each monitoring station in the seven inner-city districts to calculate a 24-hour average (8-hour average for O_3). These data were used to estimate exposures using the nearest-monitor approach in the cohort study and the inverse-distance-weighting approach in the nested case–control study for the entire pregnancy, for each trimester, and for each month of pregnancy on the basis of the gestational age and birth date of each newborn (Liu et al. 2003; Ritz and Wilhelm 2008; Woodruff et al. 2003). Logistic regressions were performed to examine the associations between individual-level dependent variables and independent variables while controlling for important covariates (Ritz et al. 2007). We focused on the effects of single pollutants and then assessed the robustness of these effects by using two-pollutant models. ORs and 95% confidence intervals (CIs) were reported. All study aims were tested based on a two-tailed significance level of 0.05. SAS 9.2 (SAS Institute, Cary, NC, USA) and R 2.7 (R Foundation for Statistical Computing, Vienna, Austria) were used for all data manipulation and statistical analysis.

In the initial stage, we created a master analytic database by merging the delivery data and questionnaire survey data with the air pollution data according to each date of birth, the duration of pregnancy, and the corresponding dates for the pollution measures. We obtained descriptive statistics (e.g., frequencies for categorical data and means, standard deviations [SDs], and minimum and maximum values for continuous data) of the adverse pregnancy outcomes, pollutant concentrations, basic demographic characteristics, and important covariates. We reviewed the data carefully so that miscoded or missing data could be identified. In dealing with outliers, caution was exercised to account for variables with skewed distributions. As a preliminary analysis, we obtained the frequencies of the outcomes according to the level of pollutants. For these univariate analyses, we stratified by each major potential effect modifier and confounder.

The dichotomous measures PTB, LBW, and IUGR were the dependent variables. We considered and controlled for covariates known or suspected to be potential confounders or effect modifiers (Ghosh et al. 2013; Ritz et al. 2007; Savitz et al. 2014). These variables included maternal age ($\leq$21, 22–35, and >35 years of age), maternal educational attainment (some middle school or below, some high school, some college, or bachelor's or higher degree), maternal occupation (professional, manual laborer, or housewife), parity (1 = mother delivering her first-born or 2 = mother with a previous live birth), gravidity (1 pregnancy or >1 pregnancies), prenatal vitamin use (yes or no), pregnancy health history (1 = hypertension, infections, or gestational complications; 0 = none), pharmaceutical use in pregnancy (yes or no), stress (yes or no), month of birth (indicator for month), infant sex (male or female), temperature at conception (normal temperature $\geq$5th [3.8°C] percentile and $\leq$95th percentile [31.6°C]) of daily mean temperatures during the study period; low temperature <5th percentile; or high temperature >95th percentile), season of conception (spring: March–May; summer: June–August; fall: September–November; or winter: December–February), total household income (<59,999 RMB, 60,000–83,999 RMB, or >84,000 RMB), exposure to cigarette smoking at home (yes or no), coal for cooking or heating used at home (yes or no), weight gain during pregnancy (below, normal, or above recommended for pre-pregnancy body-mass-index category), residence close to main roads (yes or no), SHS exposure (none, 1–10, and >10 cigarettes per day), depression during pregnancy (yes or no), and vaginal bleeding during pregnancy (yes or no).

The final models for the cohort study were adjusted for maternal age, maternal educational attainment, maternal occupation, parity, gravidity, infant sex, season of conception, and temperature at conception. The final models for the case–control study were adjusted for total household income, SHS exposure, depression during pregnancy, and vaginal bleeding during pregnancy, in addition to the variables in the cohort study. We selected these covariates in the final models based on two criteria: (1) they are known or suspected to be risk factors for the adverse pregnancy outcomes, and (2) model analyses showed that these covariates, in combination, lead to changes in the estimated effects of more than 5% for some of the study

pollutants (Ritz et al. 2007). The estimated effects of CO on PTB, for example, changed from OR = 1.07 to OR = 1.15 in Table 1.

Mother's marital status was not controlled, because nearly all mothers were married (99.9%). Types and timing of prenatal care initiation were not considered, because most of the mothers in the city had similar prenatal care services and began care early in the first trimester as required. Race and ethnicity were not controlled, because 99% of the participants were Han. Maternal smoking status and alcohol use during pregnancy were not considered in the analyses, because very few mothers were smokers (<0.7%) or drinkers (<0.5%).

One aim of our study was to assess effect modification from temperature extremes, SES, total household income, and SHS exposure on the associations between air pollution and adverse pregnancy outcomes. We tested the interactions between the study pollutants and the covariates in logistic regression models focusing on the interactions between the study pollutants and temperature extremes, family income, maternal education attainment, and SHS exposure. We also conducted a series of sensitivity analyses to test the robustness of our results. Conclusions about the associations between air pollution and adverse pregnancy outcomes were based on the covariate-adjusted regression analyses. Our power calculation is presented in Appendix K (available on the HEI Web site).

ANALYTIC STRATEGIES FOR SPECIFIC AIMS

Aim 1: To Determine Whether Elevated Ambient Concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO During Vulnerable Pregnancy Periods Are Associated with Increased Adverse Pregnancy Outcomes Adjusted for Major Risk Factors

Our principal task was to determine the relationships between each of the pollutants and adverse pregnancy outcomes using logistic regression. The dependent variables were PTB, LBW, and IUGR, defined as dichotomous categories. The independent variables were daily mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO during various vulnerable pregnancy periods over the 2-year study period from June 10, 2011, to June 9, 2013, controlling for important covariates. Unconditional logistic regression was performed to model each binary outcome variable as a function of each exposure variable (i.e., the pollutants' concentrations) and covariates (Ritz et al. 2007). We tested potential interactions between the exposure variables and the major covariates by introducing a product term into the models for each exposure variable and covariate pair. Our effect estimates represent the absolute change per unit increase in a pollutant. Based on the distributions of daily mean concentrations of pollutants, we defined the unit increases as 5 µg for PM_{10} and $PM_{2.5}$, 3 µg for NO_2 and SO_2, 10 µg for O_3, and 100 µg for CO in order to be able to compare results with those of previously published papers.

Aim 2: To Determine Whether the Associations Are Confounded by Copollutants

As an extension of the single-pollutant model as defined in Aim 1, we tested various multiple-pollutant models to check for possible pollutant confounding effects. Because of potential problems with multi-colinearity (Table 2 and Tables O.20 and O.21 in Appendix O), we focused only on two-pollutant models. The same models described above in Aim 1 were fitted to individual pollutants first, and then a second copollutant was included in each model.

Aim 3: To Determine Whether Residual Confounding Affects the Associations

We addressed this aim by using data collected from the nested case–control study. The source population was the cohort of live births taking place during the 2-year period. We selected all cases, defined as either PTB or LBW, and a comparable number of randomly sampled controls (full term [≥ 37 weeks] and normal birth weight [≥ 2500 g]) from the seven inner-city districts. Cases and controls were matched by birth month (Rogers et al. 2000). Average concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO during the specified pregnancy intervals were the independent variables. We tested effects for a wide range of important covariates during the model construction processes, as described earlier in the section on general analytic strategies and reporting.

We estimated crude and adjusted ORs for PTB and LBW in both the cohort and the nested case–control samples using single and multiple logistic regression models (Hoggatt et al. 2009; Ritz et al. 2007). The effect estimates were expressed as ORs and 95% CIs. Because PTB and LBW were lumped together into one set of cases and the mechanisms of action for PTB and LBW are different, we conducted analyses by examining each outcome separately.

We also conducted a two-phase data analysis (Hoggatt et al. 2009). Briefly, we used outcome, covariate, and exposure variables from all participants as stratification variables for the first phase. We then drew a sample of individuals with known probability from within these strata for the second phase. This effort accounted for the stratified sampling, reduced potential response and selection bias, and improved the efficiency of data analyses (Ritz et al. 2007). Details of the models are described in

Table 1. Crude and Adjusted ORs and 95% CIs for PTB, LBW, and IUGR Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy and the Most Susceptible Exposure Window (Wuhan, China; August 19, 2010–June 9, 2013)[a]

Pollutant	Period of Pregnancy[b]	Crude OR (95% CI)	Adjusted OR (95% CI)[c]
PTB			
$PM_{2.5}$	Entire pregnancy	1.02 (1.01, 1.03)	1.03 (1.02, 1.05)
	Second trimester	1.01 (1.01, 1.02)	1.02 (1.02, 1.03)
PM_{10}	Entire pregnancy	1.01 (1.00, 1.02)	1.02 (1.00, 1.04)
	Second trimester	1.01 (1.00, 1.02)	1.04 (1.03, 1.05)
SO_2	Entire pregnancy	0.98 (0.97, 1.00)	0.97 (0.96, 0.99)
	First trimester, second month, and third month[d]	0.99 (0.98, 0.99)	0.97 (0.96, 0.99)
NO_2	Entire pregnancy	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)
	First trimester and second month	0.99 (0.98, 1.00)	0.98 (0.97, 0.99)
CO	Entire pregnancy	1.07 (1.05, 1.10)	1.15 (1.11, 1.19)
	Second trimester	1.03 (1.02, 1.04)	1.10 (1.08, 1.13)
O_3	Entire pregnancy	1.03 (1.01, 1.05)	1.05 (1.02, 1.07)
	Third trimester	1.01 (1.00, 1.02)	1.04 (1.02, 1.06)
LBW			
$PM_{2.5}$	Entire pregnancy	1.01 (1.00, 1.02)	1.01 (1.00, 1.03)
	Second trimester and third month[d]	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
PM_{10}	Entire pregnancy	1.01 (0.99, 1.02)	1.01 (0.98, 1.03)
	Second trimester	1.01 (1.00, 1.02)	1.02 (1.01, 1.04)
SO_2	Entire pregnancy	1.00 (0.98, 1.01)	0.98 (0.96, 1.00)
	Third month	0.99 (0.99, 1.00)	0.98 (0.97, 0.99)
NO_2	Entire pregnancy	0.99 (0.98, 1.01)	0.98 (0.97, 1.00)
	First trimester	0.99 (0.98, 1.00)	0.98 (0.97, 0.99)
CO	Entire pregnancy	1.06 (1.03, 1.10)	1.09 (1.04, 1.13)
	Second trimester	1.03 (1.01, 1.05)	1.06 (1.03, 1.09)
O_3	Entire pregnancy	1.00 (0.98, 1.02)	1.02 (0.99, 1.05)
	Last month	1.01 (1.00, 1.02)	1.04 (1.02, 1.05)
IUGR			
$PM_{2.5}$	Entire pregnancy	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)
	First trimester	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
PM_{10}	Entire pregnancy	0.99 (0.99, 1.00)	0.99 (0.98, 1.00)
	First trimester	1.01 (1.01, 1.01)	1.01 (1.00, 1.02)
SO_2	Entire pregnancy	1.02 (1.01, 1.03)	1.03 (1.02, 1.04)
	First trimester and second trimester[d]	1.02 (1.01, 1.02)	1.02 (1.01, 1.03)
NO_2	Entire pregnancy	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)
	First trimester	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)
CO	Entire pregnancy	0.99 (0.97, 1.01)	0.98 (0.95, 1.00)
	First trimester	1.03 (1.01, 1.04)	1.03 (1.01, 1.05)
O_3	Entire pregnancy	0.99 (0.98, 1.01)	0.99 (0.97, 1.01)
	First trimester	1.00 (0.99, 1.01)	0.98 (0.97, 0.99)

[a] ORs were estimated based on per 5-μg increase in $PM_{2.5}$ and PM_{10}, 3-μg increase in NO_2 and SO_2, 10-μg increase in O_3, and 100-μg increase in CO.

[b] Entire pregnancy = from first day of conception to delivery, first trimester = first 91 days of the conception, second trimester = second 91 days of the conception, and third trimester = remaining days of pregnancy.

[c] Adjusted for maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

[d] Estimated OR refers to all listed exposure windows.

Table 2. Pearson Correlation Coefficients Among Daily Average Concentrations of Pollutants from the Closest Air-Monitoring Station in the Cohort Study (Wuhan, China; August 19, 2010–June 9, 2013)

Pollutant (μg/m^3)	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3
$PM_{2.5}$[a]	1					
PM_{10}	0.82	1				
SO_2	0.50	0.63	1			
NO_2	0.63	0.71	0.67	1		
CO	0.72	0.66	0.58	0.66	1	
O_3[b]	−0.16	−0.02	−0.13	−0.12	−0.12	1

[a] Donghu and Wujiashan monitoring stations.

[b] Daily 8-hr average concentrations (10:00 – 18:00) were used.

Appendix L. We compared the estimated ORs adjusted for covariates from the delivery dataset only with those further adjusted for covariates from the questionnaire survey (Ritz et al. 2007).

Aim 4: To Determine Whether the Associations Between Pollutant Concentrations and Adverse Pregnancy Outcomes Are Modified by Temperature Extremes, SES, or SHS Exposure

Aim 4 was addressed by including interactions in the logistic regression models. Interactions between the prespecified variables and pollutant concentrations were evaluated. We focused on interactions between a pollutant and temperature extremes at conception, family income, maternal education levels, and SHS exposure (Qian et al. 2008a; Zeka et al. 2008). The effects of the pollutant concentrations were summarized as ORs and 95% CIs.

Wuhan has been called an "oven" city because of its hot summers. Findings from our earlier PAPA program in Wuhan showed interaction effects between PM_{10} and high temperatures on daily non-accidental, cardiovascular, and cardiopulmonary mortality (Qian et al. 2008a). Examining the interaction between temperature extremes at conception and air pollution on adverse pregnancy outcomes has provided new data related to public health policy decisions. High and low temperature extremes were defined as the days when daily average temperatures were above or below the 95th or 5th percentiles, respectively, of the 2 years' data (Qian et al. 2008a).

SES is a total measure that combines an individual's occupational status and an individual's or family's economic and social position relative to those of others based on indicators of educational attainment, occupation, and income. It is difficult to measure, because so many variables exist and there are so many competing scales. One indicator by itself is not sufficient to adequately characterize SES. We therefore defined SES in two ways. First, we developed a variable for maternal educational attainment defined as four groups: some middle school or below, some high school, some college, and a bachelor's or higher degree. We also developed a variable for family income defined as four ranges: <59,999 RMB; 60,000–83,999 RMB; or >84,000 RMB. Maternal educational attainment and household income were chosen because poverty may modify the relationship between adverse pregnancy outcomes and air pollution exposure. Pollution may be associated with increased health effects in pregnant women because poorer mothers-to-be may live in areas with higher exposure, may be more susceptible to pollution, or both. Few studies have investigated the effects of poverty on the relationship between air pollution and PTB.

SHS exposure was defined as a dichotomous variable (yes or no) and a categorical variable summarizing daily numbers of cigarettes smoked. Because very few mothers (<0.1%) were smokers, the fathers' smoking defined this variable. We assessed SHS exposures by asking mothers how many cigarettes the fathers living in the household smoked during her pregnancy. SHS exposure was chosen because our previous study in Wuhan observed an association between children's respiratory symptoms and lung function and the household fuels used for cooking and heating and parental cigarette smoking (Qian et al. 2007a). In the current study, we were interested in assessing any potential interaction effects of air pollution and SHS exposure on adverse pregnancy outcomes.

Additional Analyses

We performed a wide range of sensitivity analyses to examine the robustness of our estimated effects. Our goal was to know whether the results were stable and whether they were significantly affected by decisions made during the data analyses.

In the nested case–control analyses, we performed a number of sensitivity analyses by controlling for additional questionnaire survey variables, including maternal time–activity patterns, house ventilation, whether the house directly faced a major road, pharmaceutical use history, personal care products, stress, or chronic diseases. In addition, we compared results obtained when we restricted our analyses to women who did not relocate during their pregnancy (6787 cases and controls) (Kramer et al. 1998). Women in the study relocated during pregnancy at a rate of 8.4%.

We also conducted a substudy on a group of 65,930 women (68.7% of the total study population in our cohort) to validate gestational age at birth (Hansen et al. 2008). A precise definition of PTB is essential for comparing and interpreting findings from published studies that address the health effects of exposure to air pollution (Dietz et al. 2007; Slama et al. 2008b; van den Hooven et al. 2012). Differentiation between the various methods of determining gestational age and recognition of the limitations of these methods were necessary to help achieve an understanding of the complexities of the effects of air pollution on PTB (Savitz et al. 2002; van den Hooven et al. 2012). Because our data on gestational age had been determined by ultrasound early in pregnancy (the majority of them within the first trimester) for a significant proportion of the pregnant women, we were able to determine whether the gestational age calculated by LMP from the prenatal records reflected the gestational age determined by ultrasound. The validation substudy assessed the accuracy of the PTB classifications we used in the larger study, which were based on estimated gestational age. The substudy yielded results that were similar to, but more conservative (i.e., closer to OR = 1.0) than, those for the total population.

RESULTS

AIM 1. ASSOCIATIONS BETWEEN $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, AND CO AND ADVERSE PREGNANCY OUTCOMES

We collected data for 139,486 births in the city of Wuhan during a 2-year period from June 10, 2011, to June 9, 2013 (Figure 2). After excluding 30,713 non-permanent residents of the city and 6749 births by women not living in the seven urban core districts, we had an initial pool of 102,024 births. Further exclusions were made for 962 nonviable births, 585 recorded birth defects, 48 births with extreme birth weights (<500 g or >5000 g), 3353 nonsingleton births, five with extreme gestational ages (<20 weeks or >46 weeks), and 1160 births with unclear home addresses. In some cases, a single birth met multiple exclusion criteria. From the 102,024 with qualified residential history in the study area, these exclusions left 95,911 births (94.0%) for analysis. These are the same exclusions that were applied in previously published work (Bell et al. 2007).

Daily mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO from each of the nine monitoring stations (Figure 1) are presented in Appendix M. The distributions of the concentrations from the closest air monitoring station and weather variables during the entire pregnancy of the cohort are shown in Table 3. The arithmetic mean concentrations (and minimum–maximum ranges) were 70.8 $\mu g/m^3$ (47.0 to 119.5 $\mu g/m^3$) for $PM_{2.5}$, 101.9 $\mu g/m^3$ (73.2 to 146.8 $\mu g/m^3$) for PM_{10}, 35.3 $\mu g/m^3$ (19.7 to 61.1 $\mu g/m^3$) for SO_2, 58.8 $\mu g/m^3$ (35.6 to 76.6 $\mu g/m^3$) for NO_2, 1012.4 $\mu g/m^3$ (652.9 to 1369.3 $\mu g/m^3$) for CO, and 75.0 $\mu g/m^3$ (36.3 to 145.0 $\mu g/m^3$) for O_3. These pollution ranges were wider than those in the majority of other published studies in our literature review (Brauer et al. 2008; Ebisu and Bell 2012; Gehring et al. 2014; Pereira et al. 2014; Qian et al. 2000; Savitz et al. 2014).

Table 2 shows Pearson correlation coefficients between the pollutants. The majority of the correlations were moderate, except for those with O_3. Moderate to strong positive correlations were found between all other pairs of pollutants, and reasonably high correlations were found for $PM_{2.5}$ and PM_{10}. Correlations like these can complicate regression analyses that involve the simultaneous inclusion of multiple pollutants in the models. For O_3, weak and negative correlations were found.

The final cohort study population consisted of 95,911 births after the exclusion criteria were applied (Table 4 and Figure 2). There were 4308 PTBs, 2853 LBWs, and 8452 births with IUGR; 1704 infants were both PTBs and LBWs; and 396 infants were born with all three adverse outcomes (Figures M.1 and M.2 in Appendix M). In the study population, 4.5% of births were PTBs. The majority of the cohort members were between 22 and 35 years old (90.5%), were manual laborers (70.2%), had had fewer than three pregnancies (89.7%), had had fewer than one prior live birth (81.2%), and had conceived on normal temperature days (89.55%). Slightly more than half had less than a college education, and the same fraction gave birth to males. The season of conception was approximately equally distributed

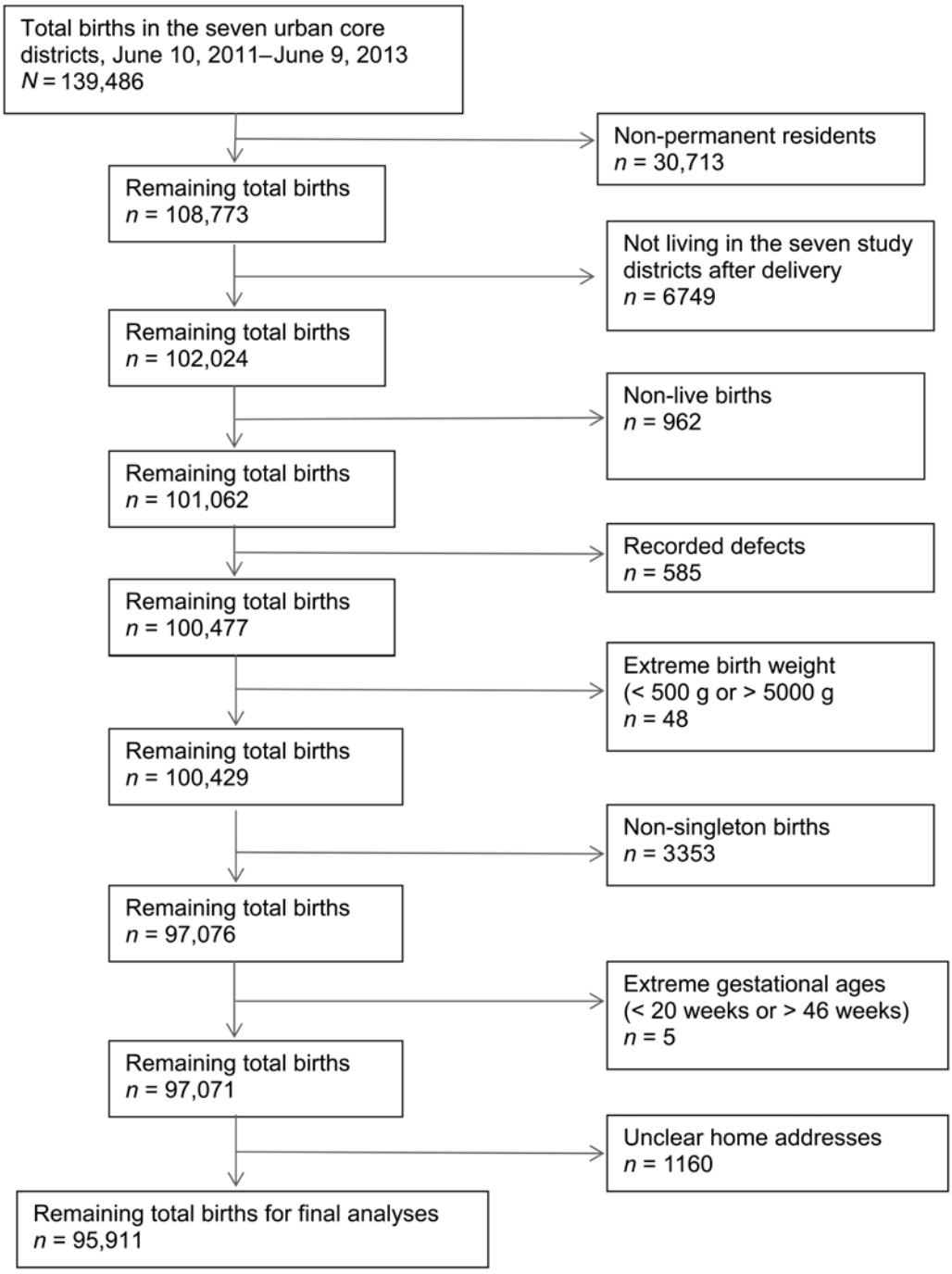

Figure 2. Flow chart for the selection of the cohort study population.

among the four seasons. Among mothers experiencing a PTB, the proportions who were ≤21 or >35 years of age, had less than a college education, had more than three prior pregnancies, had more than two prior births, gave birth to a boy, conceived in spring or fall, or conceived on normal temperature days were slightly greater than among mothers experiencing a full-term birth.

We observed small but consistent positive associations between $PM_{2.5}$, PM_{10}, CO, and O_3 and PTB during the entire pregnancy and the various susceptible exposure windows (Table 1). Every 5-μg/m^3 increase in daily mean $PM_{2.5}$ concentrations was significantly associated with an increase in PTB for exposure during the entire pregnancy (adjusted OR [aOR], 1.03; 95% CI, 1.02–1.05) and during the second trimester (aOR, 1.02; 95% CI, 1.02–1.03). Every 5-μg/m^3 increase in PM_{10} was significantly associated with an increase in PTB for exposure during the entire pregnancy (aOR, 1.02; 95% CI, 1.00–1.04) and the second trimester (aOR, 1.04; 95% CI, 1.03–1.05). Every 100-μg/m^3 increase in CO was significantly associated with an increase in PTB for exposure during the entire pregnancy (aOR, 1.15; 95% CI, 1.11–1.19) and the second trimester (aOR, 1.10; 95% CI, 1.08–1.13). Every 10-μg/m^3 increase in O_3 was significantly associated with PTB for exposure during the entire pregnancy (aOR, 1.05; 95% CI, 1.02–1.07) and the third trimester (aOR, 1.04; 95% CI, 1.02–1.06). Slightly negative associations were observed for SO_2 and PTB for exposures during the entire pregnancy (aOR, 0.97; 95% CI, 0.96–0.99) and the first trimester, second month, and third month (aOR, 0.97; 95% CI, 0.96–0.99). No significant associations were observed between PTB and NO_2 concentrations during the entire pregnancy, but a small inverse association was observed for both the first trimester and the second month (aOR, 0.98; 95% CI, 0.97–0.99).

Increases in the rates of LBW were associated with every 5-μg/m^3 increase in mean daily $PM_{2.5}$ concentrations during the entire pregnancy (aOR, 1.01; 95% CI, 1.00–1.03) as well as the second trimester and third month (aOR, 1.01; 95% CI, 1.00–1.02) (Table 5). PM_{10} exposure was significantly associated with LBW only during the second trimester (aOR, 1.02; 95% CI, 1.01–1.04). In these models, SO_2 and NO_2 concentrations both resulted in null or slightly inverse associations for LBW. Specifically, LBW was inversely associated with SO_2 exposure during the third month (aOR, 0.98; 95% CI, 0.97–0.99) and with NO_2 in the first trimester (aOR, 0.98; 95% CI, 0.97–0.99). An increase in LBW births was associated with every 100-μg/m^3 increase in CO for exposure during the entire pregnancy (aOR, 1.09; 95% CI, 1.04–1.13) and the second trimester (aOR, 1.06; 95% CI, 1.03–1.09). Every 10-μg/m^3 increase in O_3 during the last month was significantly associated with increased LBW births (aOR, 1.04; 95% CI, 1.02–1.05). As shown in Table 1, the rest of the associations were not statistically

Table 3. Average Concentrations of Pollutants from the Closest Air-Monitoring Station and Weather Variables During the Entire Pregnancy of the Cohort Study Population (Wuhan, China; August 19, 2010–June 9, 2013)

				Percentile		
Pollutant (μg/m^3)	Mean (SD)	Min	Max	25th	50th	75th
$PM_{2.5}$[a]	70.8 (14.4)	47.0	119.5	62.2	64.6	75.7
PM_{10}	101.9 (11.8)	73.2	146.8	93.4	100.3	108.4
SO_2	35.3 (6.8)	19.7	61.1	30.8	35.0	38.8
NO_2	58.8 (7.4)	35.6	76.6	53.9	59.5	63.7
CO	1012.4 (112.4)	652.9	1369.3	926.6	1014.3	1097.8
O_3[b]	75.0 (15.4)	36.3	145.0	63.5	73.2	85.3
Daily mean temperature (°C)	18.2 (3.0)	10.4	26.3	15.3	17.8	21.2
Daily mean relative humidity (%)	66.1 (3.0)	57.8	72.4	65.3	66.3	68.9

[a] Donghu and Wujiashan monitoring stations.

[b] Daily 8-hr average concentrations (10:00–18:00) were used.

Table 4. Characteristics of the Cohort Study Population, Overall and by Birth Term (Wuhan, China; August 19, 2010–June 9, 2013)

	Total Births (N = 95,911)		PTBs (N = 4,308, 4.5%)		Full-Term Births (N = 91,603, 95.5%)		
Covariate	(n)	(%)	(n)	(%)	(n)	(%)	P Values
Maternal age, years							0.01
≤ 21	4,101	4.3	204	4.7	3,897	4.2	
22–35	86,827	90.5	3,678	85.4	83,149	90.8	
> 35	4,983	5.2	426	9.9	4,557	5.0	
Maternal educational attainment							0.01
Some middle school or below	12,578	13.1	614	14.2	11,964	13.1	
Some high school	42,301	44.1	1,947	45.2	40,354	44.1	
Some college	35,395	37.0	1,489	34.6	33,906	37.0	
Bachelor's or higher degree	5,504	5.7	241	5.6	5,263	5.7	
Missing data	133	0.1	17	1.4	116	0.1	
Maternal occupation							0.01
Professionals	12,357	12.9	486	11.3	11,871	13.0	
Manual laborer	67,282	70.2	3,002	69.7	64,280	70.2	
Housewives	16,150	16.8	809	18.8	15,341	16.7	
Not reported	122	0.1	11	0.2	111	0.1	
Gravidity							0.01
1	85,995	89.7	3,732	86.6	82,263	89.8	
≥ 2	9,916	10.3	576	13.4	9,339	10.2	
Parity							0.01
1	77,924	81.2	3,233	75.0	74,691	81.6	
≥ 2	17,987	18.8	1,075	25.0	16,912	18.4	
Sex of infant							0.01
Male	51,101	53.3	2,592	60.2	48,509	53.0	
Female	44,810	46.7	1,716	39.8	43,094	47.0	
Season of conception							0.01
Winter (Dec.–Feb.)	25,406	26.5	1,096	25.5	24,310	26.5	
Spring (Mar.–May)	23,410	24.4	1,130	26.2	22,280	24.3	
Summer (June–Aug.)	22,776	23.7	974	22.6	21,802	23.8	
Fall (Sept.–Nov.)	24,319	25.4	1,108	25.7	23,211	25.4	
Temperature at conception							0.16
Low temperature	4,576	4.8	191	4.4	4,385	4.8	
Normal temperature	85,843	89.5	3,897	90.5	81,946	89.5	
High temperature	4,690	4.9	192	4.4	4,498	4.9	
Missing data	802	0.8	28	0.7	774	0.8	

significant. Sample characteristics and estimated exposures to air pollution by LBW are shown in Table M.41 in Appendix M. In the study sample, 3.0% experienced a LBW birth.

Table M.42 in Appendix M shows the characteristics of the study population by IUGR. IUGR occurred among 8.8% of study births. Estimated effects on IUGR are shown in Table 1 per 5-μg/m^3 increase in mean daily $PM_{2.5}$ and PM_{10} concentrations, 3-μg/m^3 increase in NO_2 and SO_2, 10-μg/m^3 increase in O_3, and 100-μg/m^3 increase in CO. In general, all of the pollutants' concentrations resulted in close to null associations. $PM_{2.5}$ concentrations were slightly positively associated with IUGR for exposure during the first trimester (aOR, 1.01; 95% CI, 1.00–1.02). PM_{10} was positively associated with first-trimester exposure (aOR, 1.01; 95% CI, 1.00–1.02) but was inversely associated with third-trimester exposure (aOR, 0.98; 95% CI,

0.97–0.99) (Table M.45 in Appendix M). IUGR was positively associated with SO_2 concentrations during the entire pregnancy (aOR, 1.03; 95% CI, 1.02–1.04) and the first and second trimesters (aOR, 1.02; 95% CI, 1.01–1.03). Small positive associations were observed between IUGR and CO concentrations during the first trimester (aOR, 1.03; 95% CI, 1.01–1.05). O_3 concentrations were inversely associated with first-trimester exposure (aOR, 0.98; 95% CI, 0.97–0.99) but slightly positively associated with IUGR for exposure during the next-to-last month (aOR, 1.01; 95% CI, 1.00–1.02) (Table M.45 in Appendix M). No associations for NO_2 were observed with IUGR during any pregnancy period.

AIM 2. CONFOUNDING OF THE ASSOCIATIONS BY COPOLLUTANTS

We tested for potential confounding from copollutants on the observed associations by using two-pollutant regression models (because of the moderate to strong correlations between $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO). Using more than two pollutants in the models would have generated unstable results. Because our analyses were extensive and the exposures during the entire pregnancy showed robust estimated effects in general, we focused on the effects of these exposures. The results from our two-pollutant models are shown in Table 5. The majority of the estimated effects from the two-pollutant models were similar to those from the single-pollutant models. The changes in estimated effects on PTB from the two-pollutant models were small (e.g., the OR changed from 1.03 to 1.04) (Table 5). For LBW, the results from the two-pollutant models remained, in general, almost unchanged from those from the one-pollutant models (Table 5). For the few differences found, the changes in OR were also small. For IUGR, the estimated ORs in the single-pollutant models were fairly robust, and the results also remained essentially unchanged (Table 5). It is unlikely, therefore, that the copollutants affected the associations reported in this study. Additional results are presented in Appendix N (available on the HEI Web site).

AIM 3. IMPACT OF RESIDUAL CONFOUNDING

For the nested case–control study, we compared the results of the estimated effects from the four models separately for PTB and LBW. These included models with (1) no adjustment for covariates, (2) adjustment for covariates collected with delivery data, (3) inclusion of covariates from the questionnaire plus covariates from delivery data, and (4) two phases that adjusted for covariates from both the delivery data and the questionnaire. For the two-phase analyses, in addition to controlling for detailed covariates and assessing for confounding, we accounted for stratified sampling to reduce potential selection bias and response bias by using the known sampling fractions (Hoggatt et al. 2009; Ritz et al. 2007). Because estimated effects based on the entire pregnancy exposure were generally robust and larger than the effects for other exposure periods, we focused on the entire pregnancy exposure to explore residual confounding. This focus equipped us to make comparisons between the results from the current study with those in previous studies, because the majority of the previous studies presented results based on pollutant concentrations across the entire pregnancy (Hannam et al. 2014).

We completed 7409 home visits, with a total response rate of 63.8% (Table O.22 in Appendix O). For the 6149 sampled and interviewed controls, visits were completed for 4263, for a response rate of 69.3%. For the 5457 sampled and interviewed cases, visits were completed for 3146, for a 57.7% response rate. Because the mechanisms of how air pollution affects PTB and LBW may be different, we separated PTB and LBW in our analyses. The characteristics of the study populations are shown for PTB in Table 6 and for LBW in Table O.23 in Appendix O.

We observed that adjustment for the delivery covariates had the strongest influence on the estimated effects. Adding additional covariates from the questionnaire survey to the models adjusted for the delivery covariates did not change the pollutant point estimates or the CIs. Our two-phase models also yielded similar point and interval estimates, indicating that potential selection bias and response bias were not a serious concern (Table 7). A similar pattern was obtained for the estimated effects of exposures during the various trimesters and months of pregnancy (Appendix O). In the end, we did not think the data analysis method used in Model 2 (in Table O.36 in Appendix O) was appropriate, considering that it did not take into account the potential selection bias and response bias involved in the nested case–control study (Hoggatt et al. 2009; Ritz et al. 2007). The results obtained from the model are thus questionable.

For PTB, the maximum changes in estimated effects for air pollution occurred after adjusting for covariates collected from the delivery data (comparisons between model 1 and model 2), including maternal age, educational attainment, occupation, gravidity, parity, infant sex, season of conception, and temperature at conception (Table 7). The effect estimates increased for PM_{10}, CO, and O_3 exposure across the pregnancy. After adjustment for these covariates, with the exception of SO_2 and NO_2, all of the air pollutants showed significantly positive associations with PTB. Adjusting for additional covariates collected from the questionnaire survey (comparisons between model 2 and model 3) led to small changes in the estimated effects from air pollution. The two-phase models (comparisons between model 3 and model 4) also

Table 5. Estimated ORs and 95% CIs for PTB, LBW, and IUGR Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy, Comparing One-Pollutant Models with Two-Pollutant Models (Wuhan, China; August 19, 2010–June 9, 2013)

Pollutant	PTB OR (95% CI)[a]	LBW OR (95% CI)[a]	IUGR OR (95% CI)[a]
$PM_{2.5}$	1.03 (1.02, 1.05)	1.01 (1.00, 1.03)	0.99 (0.98, 0.99)
+ PM_{10}	1.04 (1.02, 1.06)	1.01 (0.99, 1.03)	0.99 (0.97, 1.00)
+ SO_2	1.04 (1.02, 1.05)	1.01 (1.00, 1.03)	0.98 (0.97, 0.99)
+ NO_2	1.03 (1.02, 1.05)	1.01 (1.00, 1.03)	0.99 (0.98, 1.00)
+ CO	1.03 (1.01, 1.04)	1.01 (0.99, 1.02)	0.99 (0.98, 1.00)
+ O_3	1.03 (1.02, 1.04)	1.02 (0.99, 1.05)	0.99 (0.98, 1.00)
PM_{10}	1.02 (1.00, 1.04)	1.01 (0.98, 1.03)	0.99 (0.98, 1.00)
+ $PM_{2.5}$	0.99 (0.97, 1.01)	0.99 (0.97, 1.02)	1.00 (0.98, 1.02)
+ SO_2	1.03 (1.02, 1.05)	1.01 (0.99, 1.04)	0.97 (0.96, 0.99)
+ NO_2	1.02 (1.01, 1.04)	1.01 (0.99, 1.03)	0.99 (0.98, 1.00)
+ CO	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	0.99 (0.98, 1.00)
+ O_3	1.02 (1.01, 1.04)	1.01 (0.99, 1.03)	0.99 (0.97, 1.00)
SO_2	0.97 (0.96, 0.99)	0.98 (0.96, 1.00)	1.03 (1.02, 1.04)
+ $PM_{2.5}$	0.97 (0.95, 0.98)	0.98 (0.96, 1.00)	1.03 (1.02, 1.05)
+ PM_{10}	0.96 (0.94, 0.98)	0.98 (0.95, 1.00)	1.04 (1.02, 1.05)
+ NO_2	0.98 (0.96, 0.99)	0.98 (0.97, 1.00)	1.03 (1.02, 1.04)
+ CO	0.95 (0.93, 0.97)	0.97 (0.95, 0.99)	1.03 (1.02, 1.05)
+ O_3	0.98 (0.96, 1.00)	0.98 (0.96, 1.01)	1.03 (1.02, 1.04)
NO_2	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)	0.99 (0.98, 1.00)
+ $PM_{2.5}$	0.98 (0.97, 0.99)	0.98 (0.97, 1.00)	0.99 (0.98, 1.00)
+ PM_{10}	0.98 (0.97, 0.99)	0.98 (0.96, 1.00)	0.99 (0.98, 1.00)
+ SO_2	0.99 (0.97, 1.00)	0.98 (0.97, 1.00)	0.99 (0.98, 1.00)
+ CO	0.97 (0.96, 0.99)	0.98 (0.96, 0.99)	0.99 (0.98, 1.00)
+ O_3	1.00 (0.98, 1.02)	0.98 (0.96, 1.00)	0.98 (0.97, 1.00)
CO	1.15 (1.11, 1.19)	1.09 (1.04, 1.13)	0.98 (0.95, 1.00)
+ $PM_{2.5}$	1.13 (1.09, 1.17)	1.08 (1.04, 1.13)	0.98 (0.96, 1.01)
+ PM_{10}	1.14 (1.10, 1.19)	1.09 (1.04, 1.14)	0.98 (0.96, 1.01)
+ SO_2	1.18 (1.14, 1.22)	1.11 (1.06, 1.16)	0.96 (0.93, 0.99)
+ NO_2	1.16 (1.12, 1.21)	1.11 (1.05, 1.15)	0.98 (0.95, 1.01)
+ O_3	1.17 (1.13, 1.22)	1.10 (1.05, 1.15)	0.97 (0.95, 1.00)
O_3	1.05 (1.02, 1.07)	1.02 (0.99, 1.05)	0.99 (0.97, 1.01)
+ $PM_{2.5}$	1.04 (1.02, 1.07)	1.02 (0.99, 1.05)	0.99 (0.98, 1.00)
+ PM_{10}	1.05 (1.03, 1.08)	1.02 (0.99, 1.05)	0.99 (0.97, 1.01)
+ SO_2	1.04 (1.01, 1.07)	1.01 (0.98, 1.05)	1.00 (0.98, 1.02)
+ NO_2	1.05 (1.01, 1.08)	1.00 (0.96, 1.04)	0.97 (0.95, 1.00)
+ CO	1.07 (1.05, 1.10)	1.04 (1.00, 1.07)	0.99 (0.97, 1.01)

[a] Adjusted for maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

Table 6. Characteristics of the Nested Case-Control Study Population, Overall and by Birth Status (Wuhan, China; June 10, 2011–June 9, 2013)

	Total (N = 6656)		PTBs (N = 2393, 36.0%)		Controls (N = 4263, 64.0%)		
Covariate	(n)	(%)	(n)	(%)	(n)	(%)	P Value
Maternal age, years							0.01
≤ 21	259	3.9	94	3.9	16	3.9	
22–35	6016	90.4	2107	88.0	3909	91.7	
> 35	381	5.7	192	8.0	189	4.4	
Maternal educational attainment							0.96
Some middle school or below	736	11.1	264	11.0	472	11.1	
Some high school	335	45.4	121	5.1	214	5.0	
Some college	2546	38.3	929	38.8	1617	37.9	
Bachelor's or higher degree	3023	5.0	1073	44.8	1950	45.7	
Missing data	16	0.2	6	0.3	10	0.2	
Maternal occupation							0.12
Professional	804	12.1	275	11.5	529	12.4	
Blue-collar worker	4751	71.4	1727	72.2	3024	70.9	
Housewife	1096	16.4	387	16.2	709	16.6	
Not reported	5	0.1	4	0.1	1	0.01	
Gravidity							0.01
≤ 3	6069	91.2	2209	92.3	3860	90.5	
> 3	587	8.8	184	7.7	403	9.5	
Sex of infant							0.01
Male	3701	55.6	1431	59.8	2270	53.2	
Female	2955	44.4	962	40.2	1993	46.8	
Parity							0.20
1	5584	83.9	2026	84.7	3558	83.5	
≥ 2	1072	16.1	367	15.3	705	16.5	
Season of conception							0.02
Spring (Mar.–May)	1576	26.2	613	25.6	963	22.6	
Summer (June–Aug.)	1486	23.7	545	22.8	941	22.1	
Fall (Sept.–Nov.)	1851	22.3	631	26.4	1220	28.6	
Winter (Dec.–Feb.)	1743	27.8	604	25.2	1139	26.7	
Total household income (RMB)[a]							0.31
< 59,999	2986	44.9	1082	45.2	1904	44.7	
60,000–83,999	2122	31.9	737	30.8	1385	32.5	
> 84,000	1548	23.3	574	24.0	974	22.8	
SHS exposure							0.01
No	2395	36.0	811	33.9	1584	37.2	
Yes	4261	64.0	1582	66.1	2679	62.8	
Depression during pregnancy							0.23
No	6070	91.1	2169	90.6	3901	91.5	
Yes	586	8.9	224	9.4	362	8.5	
Vaginal bleeding							0.01
No	4988	74.9	1590	66.4	3398	79.7	
Yes	1668	25.1	803	33.6	865	20.3	
Temperature at conception							0.35
Low temperature	355	5.3	112	4.7	243	5.7	
Normal temperature	5954	89.5	2158	90.2	3796	89.1	
High temperature	295	4.4	105	4.4	190	4.4	
Missing data	52	0.8	18	0.7	34	0.8	

[a] The renminbi (RMB) – the official currency of China.

yielded small changes in the estimated effects. Similar results were observed for comparisons among the four models for the shorter time-interval exposures, such as months or trimesters of pregnancy (Appendix O).

Compared with the results from the cohort study, the magnitude of the estimated effects from the nested case–control study sample was slightly larger. This was caused by the use of continuous exposure variables in the cohort study and dichotomous exposure variables in the case–control study. Creating dichotomous variables from continuous variables required imposing a cut-off point, or threshold, with the assumption that values above and below the cut-off point were meaningfully different. This approach can exaggerate exposure effects between comparison groups (Vinikoor-Imler et al. 2014), or if the relationship is nonlinear (i.e., threshold-like), it can better represent the true relationship.

For LBW, a comparison of results from model 1 and model 2 showed that the maximum change in estimated effects was from OR = 1.07 to OR = 1.15 (Table 7). Adjusting for additional covariates (model 2 compared with model 3) and using the two-phase analyses (model 3 compared with model 4) both increased the estimated effects for $PM_{2.5}$, PM_{10}, CO, and O_3 exposure. Only $PM_{2.5}$ and O_3 showed significantly positive associations with LBW. Adjusting for additional covariates collected from the survey (comparisons between model 2 and model 3) led to small changes in the estimated effects. The two-phase models (comparisons between model 3 and model 4) also yielded small changes in the estimated effects. Similar small changes in effects for the comparisons were observed for the short exposure time intervals (Appendix O).

Table 7. ORs and 95% CIs Estimated from Various Models for PTB and LBW Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy in the Nested Case-Control Study (Wuhan, China; August 19, 2010–June 9, 2013)[a]

	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
Pollutant	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
PTB				
$PM_{2.5}$	1.13 (1.01, 1.26)	1.13 (1.01, 1.28)	1.15 (1.02, 1.29)	1.17 (1.04, 1.32)
PM_{10}	1.12 (1.02, 1.24)	1.17 (1.02, 1.35)	1.19 (1.03, 1.37)	1.20 (1.04, 1.38)
SO_2	1.04 (0.94, 1.15)	0.96 (0.84, 1.09)	0.94 (0.83, 1.07)	0.96 (0.85, 1.09)
NO_2	1.12 (1.02, 1.24)	1.12 (0.99, 1.26)	1.12 (0.99, 1.26)	1.09 (0.97, 1.24)
CO	1.14 (1.03, 1.26)	1.17 (1.01, 1.35)	1.19 (1.02, 1.37)	1.18 (1.02, 1.37)
O_3	1.02 (0.93, 1.12)	1.20 (1.04, 1.37)	1.19 (1.04, 1.38)	1.19 (1.03, 1.37)
LBW				
$PM_{2.5}$	1.07 (0.95, 1.20)	1.15 (1.00, 1.32)	1.16 (1.01, 1.33)	1.20 (1.05, 1.37)
PM_{10}	1.03 (0.92, 1.15)	1.05 (0.90, 1.23)	1.06 (0.90, 1.24)	1.07 (0.91, 1.25)
SO_2	1.02 (0.91, 1.14)	0.98 (0.85, 1.13)	0.97 (0.84, 1.12)	1.00 (0.87, 1.15)
NO_2	1.03 (0.92, 1.15)	1.02 (0.89, 1.17)	1.00 (0.87, 1.15)	1.01 (0.88, 1.16)
CO	1.01 (0.90, 1.13)	1.04 (0.88, 1.24)	1.05 (0.88, 1.25)	1.05 (0.88, 1.25)
O_3	1.09 (0.97, 1.22)	1.16 (0.99, 1.35)	1.17 (1.00, 1.38)	1.17 (1.00, 1.37)

[a] The cut points were values close to medians of pollutants. Specifically for PTB they were 63.7 μg/m^3 for $PM_{2.5}$, 99.5 μg/m^3 for PM_{10}, 34.9 μg/m^3 for SO_2, 58.8 μg/m^3 for NO_2, 987.5 μg/m^3 for CO, and 70.8 μg/m^3 for O_3; and for LBW they were 65.8 μg/m^3 for $PM_{2.5}$, 99.6 μg/m^3 for PM_{10}, 34.9 μg/m^3 for SO_2, 59.0 μg/m^3 for NO_2, 1014.1 μg/m^3 for CO, and 72.3 μg/m^3 for O_3.

[b] ORs were estimated as the increase in the crude odds.

[c] Adjusted for covariates from the delivery data, including maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

[d] Adjusted for covariates from the delivery data plus additional covariates from the survey, including total household income, SHS exposure, maternal depression during pregnancy, and vaginal bleeding during pregnancy.

[e] Two-phase models that adjusted for covariates from both the delivery data and survey data in model 3.

AIM 4. MODIFICATION BY TEMPERATURE EXTREMES, MATERNAL EDUCATIONAL ATTAINMENT, HOUSEHOLD INCOME, AND SHS EXPOSURE

Temperature Extremes

The estimated effects on PTB, LBW, and IUGR during the entire pregnancy by the three temperature groups (normal, low, and high) at the time of conception are summarized in Table 8. The interaction terms for temperature with $PM_{2.5}$, SO_2, O_3, and CO were statistically significant for both PTB and LBW. No clear patterns were observed for the modification of the effects by temperature extremes; the largest effects occurred either on high or low temperature days. Specifically, we found that for PTB the effects were largest when conception occurred on high temperature days for $PM_{2.5}$ (aOR, 1.08; 95% CI, 1.03–1.13) and for O_3 (aOR, 1.08; 95% CI, 0.89–1.30). It is worth noting the significant association observed for O_3 on normal temperature days (aOR, 1.07; 95% CI, 1.04–1.09), because in the unusually warm city of Wuhan, even the temperature on normal temperature days would be considered high (e.g., including days on which daily average temperatures were >30.0°C). On low temperature days, however, the largest effects were observed for SO_2 (aOR, 1.10; 95% CI, 1.01–1.18) and CO (aOR, 1.30; 95% CI, 1.08–1.58). For PM_{10} and NO_2, the interaction terms with temperature were not statistically significant.

For LBW, the largest effects occurred on high temperature days for O_3 only (aOR, 1.08; 95% CI, 0.87–1.35). On low temperature days, the largest effects occurred for $PM_{2.5}$ (aOR, 1.12; 95% CI, 0.91–1.38), SO_2 (aOR, 1.07; 95% CI, 0.98–1.17), and CO (aOR, 1.44; 95% CI, 1.15–1.80).

For IUGR, we observed statistically significant interactions with temperature for $PM_{2.5}$ and PM_{10} only. The largest effects were observed on low temperature days for $PM_{2.5}$ (aOR, 1.09; 95% CI, 0.96–1.24) and PM_{10} (aOR, 1.08; 95% CI, 1.00–1.16). No clear interaction patterns were observed for NO_2, CO, or O_3.

Maternal Educational Attainment

We did not find any statistically significant interactions for PTB and maternal educational attainment (Table 9). For LBW, we observed statistically significant (or marginally significant) interactions (Table 9). The lowest of the four educational attainment groups had the largest ORs for $PM_{2.5}$ (aOR, 1.04; 95% CI, 1.00–1.08), PM_{10} (aOR, 1.02; 95% CI, 0.97–1.08), SO_2 (aOR, 1.01; 95% CI, 0.94–1.08), and CO (aOR, 1.21; 95% CI, 1.08–1.35). The highest educational attainment group had the smallest ORs for $PM_{2.5}$ (aOR, 0.93; 95% CI, 0.87–1.00), PM_{10} (aOR, 0.92; 95% CI, 0.84–1.00), and SO_2 (aOR, 0.98; 95% CI, 0.90–1.07). The largest OR for O_3, however, occurred in the highest educational attainment group, but it was nonsignificant (aOR, 1.06; 95% CI, 0.94–1.20). All associations among the highest education group were statistically nonsignificant. NO_2 did not show any clear pattern of interaction. For IUGR, we did not find any clear pattern of interactions for $PM_{2.5}$, PM_{10}, NO_2, or CO, though the interactions were statistically significant (Table 9), except for SO_2. The biggest effect for SO_2 (aOR, 1.06; 95% CI, 1.01–1.10) occurred in the lowest educational attainment group, and the smallest effect (aOR, 0.98; 95% CI, 0.90–1.07) occurred in the highest educational attainment group. For O_3, however, the biggest effect (aOR, 1.07; 95% CI, 1.00–1.15) occurred in the highest educational attainment group, and the smaller effects occurred in the lower educational attainment groups.

Household Income

Estimated ORs and 95% CIs for PTB attributable to maternal exposure to pollutants during the entire pregnancy by total household income are shown in Table 10. For PTB, we observed significant interactions for PM_{10} and CO with household income. However, no consistent pattern of interactions was found. The largest effects, for example, occurred in the lowest income group for $PM_{2.5}$ (aOR, 1.21; 95% CI, 1.01–1.44). But the largest effects occurred in the highest income groups for PM_{10} (aOR, 1.59; 95% CI, 1.17–2.18) and NO_2 (aOR, 1.23; 95% CI, 0.94–1.61). For CO and O_3, the largest effects occurred in the middle-income group.

For LBW, significant interactions with income were observed for $PM_{2.5}$, PM_{10}, and CO (Table 10). We did not find any clear patterns of interactions.

SHS Exposure

Table 11 shows the estimated ORs and 95% CIs for PTB and LBW attributable to maternal exposure to pollutants measured across the entire pregnancy by SHS exposure level. No clear interaction patterns were observed for any of the study pollutants (Table 11). For PTB, the largest effects were observed in the highest SHS exposure groups for $PM_{2.5}$ (aOR, 1.29; 95% CI, 0.89–1.88) and O_3 (aOR, 1.59; 95% CI, 1.02–2.47), but the largest effects occurred in the no-SHS-exposure group for PM_{10} (aOR, 1.38; 95% CI, 1.14–1.67) and CO (aOR, 1.27; 95% CI, 1.04–1.54). Similar interaction patterns were observed for LBW. The largest effects were observed in the highest SHS exposure groups for $PM_{2.5}$ and O_3, but the largest effects occurred in the no-SHS-exposure groups for PM_{10} and CO. No clear interaction patterns were observed across all study pollutants. Additional results are presented in Appendix P.

Table 8. Estimated Adjusted ORs and 95% CIs for PTB, LBW, and IUGR Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy by Temperature at Conception in the Cohort Study (Wuhan, China; August 19, 2010–June 9, 2013)[a,b,c,d]

Pollutant	Normal Temperature aOR (95% CI)	Low Temperature aOR (95% CI)	High Temperature aOR (95% CI)	*P* Value[e,f]
PTB				
$PM_{2.5}$	1.03 (1.02, 1.05)	1.01 (0.85, 1.21)	1.08 (1.03, 1.13)	< 0.01
PM_{10}	1.02 (1.00, 1.04)	1.11 (1.00, 1.24)	0.94 (0.86, 1.02)	0.98
SO_2	0.97 (0.95, 0.98)	1.10 (1.01, 1.18)	0.94 (0.83, 1.06)	< 0.01
NO_2	0.98 (0.97, 1.00)	1.00 (0.94, 1.06)	0.95 (0.88, 1.03)	0.43
CO	1.14 (1.09, 1.18)	1.30 (1.08, 1.58)	1.29 (1.10, 1.51)	0.04
O_3	1.07 (1.04, 1.09)	0.92 (0.83, 1.01)	1.08 (0.89, 1.30)	< 0.01
LBW				
$PM_{2.5}$	1.01 (0.99, 1.03)	1.12 (0.91, 1.38)	1.03 (0.98, 1.08)	< 0.01
PM_{10}	1.01 (0.99, 1.03)	1.09 (0.97, 1.23)	0.89 (0.80, 0.98)	0.24
SO_2	0.98 (0.96, 1.00)	1.07 (0.98, 1.17)	0.96 (0.83, 1.11)	0.01
NO_2	0.98 (0.96, 1.00)	0.99 (0.92, 1.07)	1.02 (0.93, 1.12)	0.69
CO	1.08 (1.03, 1.13)	1.44 (1.15, 1.80)	1.04 (0.87, 1.25)	0.01
O_3	1.03 (0.99, 1.06)	0.95 (0.85, 1.06)	1.08 (0.87, 1.35)	< 0.01
IUGR				
$PM_{2.5}$	0.99 (0.98, 1.00)	1.09 (0.96, 1.24)	0.96 (0.93, 0.99)	0.04
PM_{10}	0.99 (0.98, 1.01)	1.08 (1.00, 1.16)	0.93 (0.88, 0.98)	0.02
SO_2	1.03 (1.02, 1.04)	1.01 (0.95, 1.07)	1.08 (0.98, 1.18)	0.33
NO_2	0.99 (0.98, 1.01)	1.00 (0.95, 1.04)	0.97 (0.92, 1.03)	0.48
CO	0.98 (0.95, 1.01)	0.99 (0.87, 1.14)	1.01 (0.91, 1.12)	0.76
O_3	0.98 (0.96, 1.00)	1.01 (0.94, 1.08)	0.94 (0.83, 1.07)	0.15

[a] ORs were estimated based on per 5-μg increase in $PM_{2.5}$ and PM_{10}, 3-μg increase in NO_2 and SO_2, 10-μg increase in O_3, and 100-μg increase in CO.

[b] Adjusted for maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

[c] Normal temperature ≥ 5th (3.8°C) percentile and ≤ 95th percentile (31.6°C) of daily average temperatures during the study period; low temperature < 5th percentile; and high temperature > 95th percentile.

[d] Temperature was defined as the daily average temperatures in the week of conception with the estimated conception day in the middle.

[e] Estimates were obtained for the main effects and for the pollutant × temperature interaction models.

[f] For the interaction term for the three temperature groups.

Table 9. Estimated Adjusted ORs and 95% CIs for PTB, LBW, and IUGR Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy by Maternal Educational Attainment in the Cohort Study (Wuhan, China; August 19, 2010–June 9, 2013)[a,b]

	Below Middle School	Some High School	Some College	Bachelor's or Higher	
Pollutant	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	*P* Value[c]
PTB					
$PM_{2.5}$	1.06 (1.03, 1.10)	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	1.02 (0.97, 1.08)	0.56
PM_{10}	1.06 (1.01, 1.11)	1.03 (1.00, 1.05)	1.01 (0.98, 1.04)	0.99 (0.93, 1.07)	0.55
SO_2	0.99 (0.94, 1.05)	0.98 (0.95, 1.00)	0.97 (0.94, 1.00)	0.98 (0.91, 1.06)	0.39
NO_2	1.00 (0.96, 1.04)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.94, 1.05)	0.56
CO	1.23 (1.11, 1.35)	1.12 (1.06, 1.18)	1.16 (1.09, 1.24)	1.18 (1.00, 1.39)	0.76
O_3	1.04 (0.96, 1.12)	1.06 (1.02, 1.10)	1.05 (1.00, 1.09)	1.03 (0.93, 1.14)	0.59
LBW					
$PM_{2.5}$	1.04 (1.00, 1.08)	0.99 (0.97, 1.02)	1.03 (1.01, 1.06)	0.93 (0.87, 1.00)	0.04
PM_{10}	1.02 (0.97, 1.08)	1.00 (0.97, 1.03)	1.02 (0.99, 1.06)	0.92 (0.84, 1.00)	0.04
SO_2	1.01 (0.94, 1.08)	0.98 (0.95, 1.01)	0.98 (0.95, 1.02)	0.98 (0.90, 1.07)	0.06
NO_2	0.99 (0.94, 1.03)	0.99 (0.96, 1.01)	0.98 (0.95, 1.01)	0.98 (0.91, 1.04)	0.04
CO	1.21 (1.08, 1.35)	1.01 (0.95, 1.08)	1.17 (1.08, 1.27)	1.02 (0.84, 1.24)	0.03
O_3	1.00 (0.91, 1.09)	1.03 (0.98, 1.08)	1.01 (0.96, 1.06)	1.06 (0.94, 1.20)	0.04
IUGR					
$PM_{2.5}$	0.97 (0.95, 0.99)	0.99 (0.97, 1.00)	1.00 (0.98, 1.02)	0.93 (0.89, 0.97)	0.01
PM_{10}	0.98 (0.94, 1.01)	0.98 (0.97, 1.00)	1.01 (0.98, 1.03)	0.92 (0.84, 1.00)	0.01
SO_2	1.06 (1.01, 1.10)	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)	0.98 (0.90, 1.07)	0.01
NO_2	1.00 (0.97, 1.03)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)	0.98 (0.91, 1.04)	0.01
CO	0.97 (0.90, 1.04)	0.97 (0.94, 1.01)	1.00 (0.96, 1.05)	0.90 (0.80, 1.02)	0.01
O_3	0.99 (0.94, 1.05)	0.98 (0.95, 1.01)	0.99 (0.96, 1.02)	1.07 (1.00, 1.15)	0.01

[a] ORs were estimated based on per 5-μg increase in $PM_{2.5}$ and PM_{10}, 3-μg increase in NO_2 and SO_2, 10-μg increase in O_3, and 100-μg increase in CO.

[b] Adjusted for maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

[c] For the interaction term for the four groups of maternal education attainment.

Table 10. Estimated Adjusted ORs and 95% CIs for PTB and LBW Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy by Total Household Income in the Nested Case-Control Study (Wuhan, China; August 19, 2010–June 9, 2013)[a,b]

	12,000–59,999 RMB[c]	60,000–83,999 RMB	> 84,000 RMB	
Pollutant	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	*P* Value
PTB				
$PM_{2.5}$	1.21 (1.01, 1.44)	1.17 (0.94, 1.46)	1.13 (0.88, 1.46)	0.10
PM_{10}	1.19 (0.96, 1.47)	1.11 (0.86, 1.44)	1.59 (1.17, 2.18)	0.01
SO_2	0.97 (0.80, 1.18)	0.96 (0.76, 1.21)	1.02 (0.78, 1.34)	0.57
NO_2	1.11 (0.92, 1.34)	1.10 (0.88, 1.37)	1.23 (0.94, 1.61)	0.70
CO	1.13 (0.90, 1.40)	1.35 (1.02, 1.77)	1.21 (0.89, 1.65)	0.01
O_3	1.11 (0.90, 1.38)	1.36 (1.05, 1.76)	1.12 (0.82, 1.52)	0.29
LBW				
$PM_{2.5}$	1.21 (0.99, 1.48)	1.11 (0.86, 1.42)	1.35 (1.02, 1.80)	0.01
PM_{10}	0.94 (0.75, 1.19)	0.99 (0.74, 1.34)	1.63 (1.16, 2.29)	0.02
SO_2	0.94 (0.76, 1.16)	1.03 (0.79, 1.35)	1.03 (0.76, 1.41)	0.49
NO_2	0.91 (0.74, 1.11)	1.09 (0.84, 1.40)	1.20 (0.88, 1.62)	0.73
CO	0.89 (0.69, 1.15)	1.28 (0.92, 1.78)	1.26 (0.87, 1.82)	0.01
O_3	1.14 (0.91, 1.44)	1.29 (0.96, 1.73)	1.10 (0.77, 1.57)	0.90

[a] Adjusted for covariates from the delivery data plus additional covariates from the survey, including total household income, SHS exposure, depression during pregnancy, and vaginal bleeding during pregnancy.

[b] The cut points were values close to medians of pollutants. Specifically for PTB they were 72.3 μg/m^3 for $PM_{2.5}$, 105.9 μg/m^3 for PM_{10}, 34.1 μg/m^3 for SO_2, 60.2 μg/m^3 for NO_2, 967.0 μg/m^3 for CO, and 70.8 μg/m^3 for O_3; and for LBW they were 64.0 μg/m^3 for $PM_{2.5}$, 99.2 μg/m^3 for PM_{10}, 35.4 μg/m^3 for SO_2, 59.0 μg/m^3 for NO_2, 1011.3 μg/m^3 for CO, and 72.4 μg/m^3 for O_3.

[c] RMB = renminbi (official currency of China).

Additional Analyses

To assess the accuracy of the gestational age at birth as estimated from prenatal records using the date of the first day of the LMP, we compared it with the age as estimated from ultrasound examination during the first trimester, the gold standard for measuring when pregnancy begins. We conducted this substudy on the 65,930 participants (68.7% of the total cohort study population) whose dates of conception and expected delivery were estimated by ultrasound during the first trimester. Using the data from only these participants, our results for the pollutants and pregnancy outcomes were similar to, but more conservative (i.e., closer to OR = 1.0) than, those for the total study population (Table 12 compared with Table 1).

To test whether maternal relocation during pregnancy significantly affected our effects estimates, we did sensitivity analyses with the group of women (6787 cases and controls) who did not relocate during pregnancy. The resulting effects estimates were similar to those obtained using the entire case–control study sample (Table 7 and Table 13).

Birth weight among full-term infants only may be a better outcome variable than simple LBW for examining associations between air pollution and adverse pregnancy outcomes, because it removes the effects of prematurity. Consequently we reanalyzed our data in the manner used by Pedersen and colleagues (2013), including only the full-term births and dichotomizing by low birth weight (<2500 g) versus not low birth weight. Results are shown in column 2 of Table M.49 in Appendix M. Differences in the estimated effects between using term LBW among the full-term infants only and the standard LBW among all infants (term and preterm) were small (Table M.49). The exception was for CO, where statistically significant effects became nonsignificant and the estimated OR changed from 1.09 to 1.02. We also analyzed the data using birth weight as a continuous variable for the full-term infants only. The assumptions of normality were not met, but the results are nonetheless presented in the last column of Table M.49.

We also analyzed the data with both birth weight (in grams) and gestational age (in days) as continuous variables. The results are shown in Table M.50 and Table M.51

Table 11. Estimated Adjusted ORs and 95% CIs for PTB and LBW Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy by Dose of Paternal Cigarette Smoking in the Nested Case-Control Study (Wuhan, China; August 19, 2010–June 9, 2013)[a,b]

	None	1–10[c]	> 10[c]	
Pollutant	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	*P* Value[d]
PTB				
$PM_{2.5}$	1.18 (1.01, 1.39)	1.08 (0.87, 1.35)	1.29 (0.89, 1.88)	0.52
PM_{10}	1.38 (1.14, 1.67)	1.14 (0.88, 1.48)	0.93 (0.60, 1.43)	0.17
SO_2	1.00 (0.85, 1.19)	1.00 (0.79, 1.25)	0.67 (0.46, 1.00)	0.14
NO_2	1.14 (0.97, 1.35)	1.18 (0.94, 1.48)	0.98 (0.68, 1.43)	0.30
CO	1.27 (1.04, 1.54)	1.13 (0.86, 1.49)	1.08 (0.69, 1.69)	0.63
O_3	1.22 (1.01, 1.48)	1.00 (0.77, 1.30)	1.59 (1.02, 2.47)	0.24
LBW				
$PM_{2.5}$	1.25 (1.04, 1.50)	1.00 (0.77, 1.29)	1.48 (0.98, 2.22)	0.44
PM_{10}	1.22 (0.98, 1.51)	0.84 (0.63, 1.13)	1.06 (0.66, 1.70)	0.42
SO_2	0.52 (0.37, 0.74)	0.43 (0.27, 0.69)	0.62 (0.27, 1.43)	0.56
NO_2	1.02 (0.85, 1.22)	1.06 (0.82, 1.37)	0.89 (0.59, 1.35)	0.38
CO	1.21 (0.96, 1.52)	0.94 (0.68, 1.30)	0.82 (0.49, 1.39)	0.56
O_3	1.18 (0.96, 1.46)	1.12 (0.83, 1.51)	1.37 (0.85, 2.20)	0.37

[a] Adjusted for covariates from the delivery data plus additional covariates from the survey, including total household income, SHS exposure, depression during pregnancy, and vaginal bleeding during pregnancy.

[b] The cut points were values close to medians of pollutants. Specifically for PTB they were 68.1 μg/m^3 for $PM_{2.5}$, 97.0 μg/m^3 for PM_{10}, 30.2 μg/m^3 for SO_2, 61.4 μg/m^3 for NO_2, 953.6 μg/m^3 for CO, and 73.0 μg/m^3 for O_3; and for LBW they were 63.2 μg/m^3 for $PM_{2.5}$, 98.0 μg/m^3 for PM_{10}, 38.4 μg/m^3 for SO_2, 62.1 μg/m^3 for NO_2, 1010.3 μg/m^3 for CO, and 69.6 μg/m^3 for O_3.

[c] The unit of SHS exposure during pregnancy is cigarettes/day.

[d] For the interaction term for the three groups of paternal smoking amount.

in Appendix M. Although the results from the logistic regressions were, in general, comparable with those from the linear regressions for gestational age in days, discrepancies in the estimated effects for some pollutants were found. For example, both linear and logistic regression yielded a positive OR and positive beta for the estimated effects of O_3 on gestational age (Table M.50). For birth weight, results from the two models were consistent only for $PM_{2.5}$ and CO. Most of the estimated effects were small and nonsignificant (Table M.51).

We do not think the selection of controls was a factor that caused the discrepancies, because we took into account the random sampling of the controls from the cohort in our two-phase analysis. This effort used inverse probability weighting to adjust for missing covariates among those who were not selected into the nested case–control study. The discrepancy in the estimated effects between the two methods might have been caused in part by the difference in the nature of the outcome variables (continuous or dichotomous), the statistical method used, or the assumptions underpinning the models. In the end, we used the logistic regression models instead of the linear regression models, because the assumption of a normal distribution of outcome variables did not hold, and the assumption of a linear relationship between exposures and outcomes was not met. Savits and colleagues (2014) also

Table 12. Estimated ORs and 95% CIs for PTB, LBW, and IUGR Attributable to Maternal Exposure to Pollutants During the Entire Pregnancy for 65,930 Women Whose Gestational Ages were Diagnosed by Ultrasound Examinations in the First Trimester of Pregnancy in the Cohort Study (Wuhan, China; August 19, 2010–June 9, 2013)[a]

Pollutant	Crude OR (95% CI)	Adjusted OR (95% CI)[b]
PTB		
$PM_{2.5}$	1.01 (1.00, 1.03)	1.02 (1.01, 1.04)
PM_{10}	1.00 (0.99, 1.02)	1.00 (0.98, 1.03)
SO_2	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)
NO_2	1.00 (0.98, 1.01)	1.00 (0.98, 1.01)
CO	1.04 (1.00, 1.08)	1.07 (1.02, 1.12)
O_3	1.00 (0.97, 1.02)	1.00 (0.96, 1.03)
LBW		
$PM_{2.5}$	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)
PM_{10}	1.02 (1.00, 1.04)	1.01 (0.98, 1.04)
SO_2	1.01 (0.99, 1.03)	0.99 (0.96, 1.02)
NO_2	1.01 (0.99, 1.03)	1.00 (0.98, 1.03)
CO	1.04 (1.00, 1.09)	1.02 (0.96, 1.08)
O_3	0.95 (0.92, 0.98)	0.96 (0.92, 1.00)
IUGR		
$PM_{2.5}$	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)
PM_{10}	0.99 (0.99, 1.00)	0.99 (0.97, 1.00)
SO_2	1.02 (1.01, 1.03)	1.03 (1.02, 1.04)
NO_2	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)
CO	0.99 (0.97, 1.01)	0.98 (0.95, 1.00)
O_3	0.99 (0.98, 1.01)	0.99 (0.97, 1.01)

[a] ORs were estimated based on per 5-μg increase in $PM_{2.5}$ and PM_{10}, 3-μg increase in NO_2 and SO_2, 10-μg increase in O_3, and 100-μg increase in CO.

[b] Adjusted for maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

observed a nonlinear relationship between term birth weight and NO_2 exposure. Using the linear regression models, then, could have twisted the relationships.

To obtain an insight into the possible shapes of the relationships between the pollutants and the adverse pregnancy outcomes, we analyzed the data into tertiles (i.e., the top, middle, and bottom thirds of each pollutant's concentration range). The results are shown in Tables M.54–M.59 in Appendix M; they indicated an exposure–response relationship for $PM_{2.5}$ and both PTB and LBW only. Positive associations and/or the largest ORs at the highest concentrations remained for PTB with $PM_{2.5}$, PM_{10}, CO, and O_3 as well as for LBW with $PM_{2.5}$, PM_{10}, and CO; negative associations were observed. Pedersen and colleagues (2013) also reported that the observed positive associations between term LBW and $PM_{2.5}$ remained when restricting the population to three exposure groups. The authors did not report any similar data analyses for SO_2, NO_2, CO, PM_{10}, or O_3, and as a result we could not make direct comparisons. Our results indicated that nonlinear relationships might exist for SO_2 and NO_2, which is similar to what Savitz and colleagues (2014) reported.

Table 13. Estimated ORs and 95% CIs for PTB and LBW Attributable to Maternal Exposure to Pollutants During Entire Pregnancy for 6,787 Cases and Controls Who Did Not Relocate During Pregnancy in the Nested Case-Control Study (Wuhan, China; August 19, 2010–June 9, 2013)[a]

	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
Pollutant	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
PTB				
$PM_{2.5}$	1.10 (0.98, 1.23)	1.11 (0.98, 1.26)	1.12 (0.99, 1.27)	1.14 (1.01, 1.29)
PM_{10}	1.11 (1.00, 1.23)	1.16 (1.00, 1.35)	1.17 (1.01, 1.36)	1.19 (1.02, 1.38)
SO_2	1.03 (0.92, 1.14)	0.95 (0.84, 1.09)	0.93 (0.82, 1.07)	0.95 (0.84, 1.08)
NO_2	1.09 (0.98, 1.21)	1.07 (0.94, 1.22)	1.07 (0.94, 1.21)	1.07 (0.94, 1.22)
CO	1.13 (1.01, 1.25)	1.17 (1.01, 1.36)	1.20 (1.03, 1.40)	1.20 (1.04, 1.40)
O_3	1.06 (0.95, 1.17)	1.21 (1.04, 1.39)	1.21 (1.04, 1.40)	1.21 (1.05, 1.40)
LBW				
$PM_{2.5}$	1.11 (0.98, 1.27)	1.13 (0.98, 1.30)	1.14 (0.98, 1.31)	1.14 (0.99, 1.31)
PM_{10}	1.01 (0.90, 1.14)	1.03 (0.87, 1.21)	1.03 (0.87, 1.22)	1.05 (0.89, 1.24)
SO_2	0.99 (0.88, 1.12)	0.95 (0.82, 1.10)	0.94 (0.81, 1.09)	0.93 (0.78, 1.11)
NO_2	1.03 (0.91, 1.16)	1.02 (0.88, 1.18)	1.00 (0.87, 1.16)	1.01 (0.88, 1.17)
CO	1.02 (0.90, 1.15)	1.06 (0.89, 1.27)	1.07 (0.89, 1.28)	1.07 (0.90, 1.28)
O_3	1.07 (0.95, 1.20)	1.12 (0.95, 1.32)	1.13 (0.96, 1.34)	1.12 (0.96, 1.32)

[a] The cut points were values close to medians of pollutants. Specifically for PTB they were 63.7 μg/m³ for $PM_{2.5}$, 96.6 μg/m³ for PM_{10}, 34.9 μg/m³ for SO_2, 58.8 μg/m³ for NO_2, 987.5 μg/m³ for CO, and 70.8 μg/m³ for O_3; and for LBW they were 63.5 μg/m³ for $PM_{2.5}$, 99.1 μg/m³ for PM_{10}, 34.9 μg/m³ for SO_2, 58.9 μg/m³ for NO_2, 1010.8 μg/m³ for CO, and 72.3 μg/m³ for O_3.

[b] ORs were estimated as the increase in the crude odds.

[c] Adjusted for covariates from the delivery data, including maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and temperature at conception.

[d] Adjusted for covariates from the delivery data plus additional covariates from the survey, including total household income, SHS exposure, depression during pregnancy, and vaginal bleeding during pregnancy.

[e] Two-phase models that adjusted for covariates from both the delivery data and survey data in model 3.

DISCUSSION AND CONCLUSIONS

SUMMARY OF FINDINGS

We explored our four hypotheses using both a prospective cohort study and a nested case–control study design. We found small but consistently positive associations between $PM_{2.5}$, PM_{10}, CO, or O_3 concentrations across the entire pregnancy and both PTB and LBW. We observed negative associations for SO_2 or NO_2 and both PTB and LBW, although the ORs were close to the null, and some were not statistically significant. The majority of the estimated effects from our two-pollutant models were similar to those estimated from single-pollutant models. The associations found upon controlling for the covariates collected at delivery appeared not to be biased by residual confounding. No critical exposure windows were identified consistently. The largest effect for PTB, for example, was for the second trimester for $PM_{2.5}$, PM_{10}, and CO. But for SO_2 the largest effect was for the first trimester, second month, and third month. For NO_2 it was the first trimester and second month, and for O_3 the third trimester. We also examined temperature extremes, maternal educational attainment, household income, and SHS exposure as effect modifiers. No clear patterns were observed for the modification of temperature extremes, though enhanced effects were observed for both low and high temperature days. The largest effect of $PM_{2.5}$ on PTB, for example, was for high temperature days. For maternal educational attainment, we did not find any statistically significant interactions for PTB. In general, women with lower attainment had a higher rate of LBW associated with $PM_{2.5}$, PM_{10}, and

CO than those with higher attainment. No clear patterns of interaction were observed for SO_2, NO_2, or O_3. We did not find any consistent interaction pattern for IUGR for any pollutant. For household income, we did not find any clear pattern of interactions between the study pollutants and either PTB or LBW, although statistically significant interactions were found. In conclusion, we observed adverse effects from air pollution on adverse pregnancy outcomes. In general, pregnant women exposed to temperature extremes at conception were particularly susceptible to air pollution. These conclusions are supported by the agreement in results across the two study designs we used.

There were several unique aspects to our study. First, it was a population-based cohort study from which nested case and control samples were drawn. The nested case–control design, which is less likely to suffer selection bias, was an efficient and cost-effective strategy to assess the effects of air pollution on adverse pregnancy outcomes. It allowed the collection of additional information about covariates for the 7409 cases and controls than would have been practical for the full cohort sample. The additional information enhanced our ability to assess residual confounding. In addition, the study was, to our knowledge, the only prospective cohort study done in China assessing air pollution effects on adverse pregnancy outcomes. Furthermore, the population has been stable — the pollution levels were higher and the range of exposures was wider than those reported in most of the published literature. These features made the sample ideal for the exploration of associations between exposures and adverse pregnancy outcomes. Lastly, the study city is known as an "oven" city because the region experiences extremely high temperatures every summer yet still experiences cold winters. This feature provided an opportunity to explore the effect modification of temperature extremes. The observed enhanced pollution effects on adverse pregnancy outcomes from both high and low temperatures at conception have provided important new evidence.

We found small but consistently positive associations between $PM_{2.5}$, PM_{10}, CO, or O_3 concentrations across the entire pregnancy and both PTB and LBW. These results were generally consistent with previous findings and are robust (Brauer et al. 2008; Fleischer et al. 2014; Pedersen et al. 2013; Ritz et al. 2007; Savitz et al. 2014). A series of sensitivity analyses and subset analyses allowed adjustments for a number of additional variables taken from the questionnaire survey, including household income, SHS exposure, maternal depression, chronic medical conditions, vaginal bleeding during pregnancy, and pregnancy weight gain. Adjustment for these variables in our model analyses did not change the estimated effects appreciably. We also performed two-phase model analyses to correct for potential response bias or selection bias and to increase our efficiency in estimating effects. The two-phase analyses yielded similar effects, indicating that potential response bias or selection bias were not a concern for this study. Our data analyses were extended to include only women who reported that they had not changed residence during pregnancy. The estimated effects were similar to those when using the complete nested case–control sample. The similarity in effects may have been caused by the fact that those who did not relocate during pregnancy were less affected by exposure misclassification and the fact that any misclassification of exposure status among those who did relocate would have been nondifferential (Ritz et al. 2007). We also restricted our analyses to women whose gestational age was diagnosed by early ultrasound examinations to explore potential misclassification of PTB status, and the results, again, remained similar.

BIOLOGICAL PLAUSIBILITY

We are not entirely clear about the biological mechanisms involved in pollutant effects on pregnancy outcomes. Several hypotheses exist (Kannan et al. 2006). Direct toxic effects of pollutants may retard fetal growth, either by fetal hypoxia caused by placental vasoconstriction or fetal carboxyhemoglobin (Longo 1977; Salmasi et al. 2010), similar to the effects of smoking tobacco (Ritz and Yu 1999). Pollutants may also interfere with the transportation of oxygen and nutrients within the placenta because of the consequences of hemodynamic responses, coagulation, systemic inflammation, oxidative stresses, or impaired endothelial function (Angiolini et al. 2006; Kannan et al. 2006; Risom et al. 2005; Slama et al. 2008a). For example, exposures related to metals, such as aluminum and titanium, may lead to increased oxidative stress burdens, which can in turn cause adverse pregnancy outcomes (Wei et al. 2009). Air pollution could also compromise the general health of women through airway inflammation, which may lead to systemic effects or affect the fetus through oxidative stress (Glinianaia et al. 2004). This pathway is probably significant, because pregnant women have higher ventilation rates. Inflammatory cytokines and lipid peroxidation species generated in the inflammation processes could affect fetal growth (Knuckles and Dreher 2007; Salam et al. 2005). Pollutants could also induce DNA adducts (Sram et al. 2005). Fetuses may be more susceptible to genetic damage than adults, and increased DNA adducts in a fetus could lead to decreased levels of DNA repair efficiency and detoxification enzymatic efficiency (Kannan et al. 2006; Myllynen et al. 2005; Wyatt et al. 1998). DNA adducts could be generated when polycyclic aromatic hydrocarbons (PAHs) are adsorbed

onto the surface of the PM (Parker et al. 2005). DNA adducts were also associated with decreased length of gestation (Liu et al. 2003; Topinka et al. 2009). Animal study data have been sparse (Rocha et al. 2008; Tsukue et al. 2002). Female mice exposed to urban air pollution during pregnancy showed inhibited fetal growth (Veras et al. 2008), and their offspring showed reduced birth weight (Rocha et al. 2008) and inhibited lung growth (Mauad et al. 2008).

In Wuhan, motor vehicle engine combustion is the principal source of fine and ultrafine particles, such as $PM_{2.5}$, in the urban atmosphere (Hitchins et al. 2000). In addition to fine particles, $PM_{2.5}$ includes ultrafine particles — of various chemical and physical compositions — with a low mass but a high surface area that can adsorb harmful components, such as PAHs (Sioutas et al. 2005). $PM_{2.5}$ may affect fetal growth through multiple, complex biological pathways. Maternal exposure to $PM_{2.5}$ could transfer toxic components across the placenta to the fetus from $PM_{2.5}$ accumulated in the mothers' lungs (Dejmek et al. 2000; Roberts et al. 1991; Veras et al. 2008). These toxic components, transferred from $PM_{2.5}$, could lead to changes in placental development and subsequent nutrient and oxygen delivery to the fetus, blood coagulation, hemodynamic responses, endothelial function, oxidative stress and inflammation, heart-rate variability, and alteration in cardiac function of pregnant women (Ritz and Wilhelm 2008). Previous studies have also suggested that DNA-adduct levels of PAHs in cord-blood leukocytes were associated with small head circumferences and LBW (Perera et al. 2003).

We observed small but consistent positive associations between $PM_{2.5}$, PM_{10}, CO, or O_3 and adverse pregnancy outcomes. These findings are supported by major studies in North America and Europe, which indicated that $PM_{2.5}$ was positively associated with adverse outcomes (Basu et al. 2004; Fleischer et al. 2014; Morello-Frosch et al. 2010; Parker et al. 2005; Pedersen et al. 2013; Rich et al. 2009; Savitz et al. 2014; Wilhelm and Ritz 2005), even though the $PM_{2.5}$ concentrations in those studies were much lower than those in the current study. The mean concentration of $PM_{2.5}$ during the entire pregnancy in this study was 70.8 $\mu g/m^3$. The studies in North America and Europe had much lower mean $PM_{2.5}$ concentrations; when reported, the mean concentrations ranged from 5.3 $\mu g/m^3$ in Vancouver, British Columbia, Canada (Brauer et al. 2008), to 20.0 $\mu g/m^3$ in Los Angeles County, California, USA (Ritz et al. 2007). Other studies, however, detected no associations, and even slightly protective associations, between $PM_{2.5}$ and LBW or IUGR (Vinikoor-Imler et al. 2014). This finding is similar to that of another study conducted among 22 countries by the World Health Organization Global Survey, which reported that $PM_{2.5}$ concentrations were not associated with PTB (Fleischer et al. 2014). Pedersen and colleagues (2013) examined data from 14 cohorts in 12 European countries and observed statistically significant effects (OR, 1.18; 95% CI, 1.06–1.33) on LBW (using LBW among full-term infants) for a 5-$\mu g/m^3$ increase in $PM_{2.5}$.

CO may be a good surrogate for motor vehicle exhaust (Ritz and Wilhelm 2008; Wilhelm and Ritz 2003). It could also be a surrogate for other pollutants, including those emitted from vehicles and other combustion sources. CO is heterogeneous spatially, and measures at monitoring stations may only reflect concentrations within a short distance of the station (Woodruff et al. 2009). The consistent associations we observed between CO and adverse outcomes suggest that local vehicle exhaust products may play an important role in the urban core area of the study city. Inspired CO may combine with oxygen on hemoglobin-binding sites, limiting the delivery of oxygen, causing fetal hypoxia (Maisonet et al. 2004). CO could also trigger an abnormal reaction between trophoblasts and uterine tissue in the early stages of pregnancy, leading to abnormal fetal growth (Shah and Balkhair 2011), and could possibly injure the endothelium through an oxidative process (Hardy and Thom 1994).

O_3 is a photochemical pollutant formed by the reactions of volatile organic compounds with nitrogen oxides (NO_x) in the presence of sunlight. Homogeneously distributed in areas, it could be a plausible contributor to an inflammatory response (Mudway et al. 1999) and could interfere with fetal neurodevelopment, leading to PTB or LBW (Dell'Omo et al. 1995). Toxicology studies have shown that O_3 is one of the major species involved in the development of oxidative stress. Larini and Bocci (2005) reported that O_3 exposure was associated with increases in both lipid peroxidation products and inflammatory cytokines.

We examined two-pollutant models to tease out the effects between the regional pollutants (O_3, $PM_{2.5}$, and SO_2) and the local pollutants (CO, PM_{10}, and NO_2). The positive associations observed for O_3 in the single-pollutant models remained in the two-pollutant models, indicating that the observed O_3 effects were unlikely to be affected by either regional or local pollutants. Our findings for the positive associations of O_3 are also supported by studies conducted in North America (Darrow et al. 2009; Laurent et al. 2013; Morello-Frosch et al. 2010; Salam et al. 2005; Vinikoor-Imler et al. 2014; Wilhelm and Ritz 2005). Lower O_3 concentrations were present in the studies conducted in California (Laurent et al. 2013; Morello-Frosch et al. 2010), North Carolina (Vinikoor-Imler et al. 2014), and Georgia (Darrow et al. 2009) than in our study. A study in Texas also reported a positive association between O_3 and LBW (Geer et al. 2012). In contrast, no associations were reported from studies conducted mainly outside of the United States. Brauer and colleagues (2008), for example,

found that all study pollutants except O_3 were associated with IUGR in Vancouver, Canada. Liu and colleagues (2003) reported a similar null association in the same city.

NO_2, a secondary pollutant, is usually less affected by regional pollution sources (Savitz et al. 2014). Monitor-based estimates may be appropriate for estimating NO_2 exposure (Brauer et al. 2008). NO_2 could affect the fetus directly; it may also retard fetal development by inhibiting placental vascular function (Clifton et al. 2001; Veras et al. 2008) and suppressing antioxidant defense systems (Tabacova et al. 1998). Animal studies are sparse, but one study did show that exposure to NO_2 during pregnancy induced lipid peroxidation in the placenta (Tabacova et al. 1998). Further studies into biological mechanisms are warranted.

SO_2, emitted mainly from industrial coal combustion, is also a regional pollutant with less spatial heterogeneity. SO_2 exposure could lead to functional and developmental toxicities for the fetus (Shah and Balkhair 2011; Singh 1989). Reactive oxygen species generated in the cell can lead to oxidative stress, ptosis, or even necrosis as a result of interaction between SO_2 and NO_x (Vadillo-Ortega et al. 2014). Kannan and colleagues (2006) hypothesized that reactive sulfur species could affect antioxidants and enzymes as an oxidative stressor and inhibit growth and development of the embryo.

In general, we found null or slightly inverse associations between PTB, LBW, or IUGR and both NO_2 and SO_2. These outcomes were associated with CO, and the associations did not change after adjustment for SO_2. Fewer studies have focused on SO_2, and few of those have found consistent results. Stieb and colleagues (2012) reviewed 62 and found that the estimated pooled effects of SO_2 on PTB and LBW were less consistent than those of other pollutants, such as $PM_{2.5}$ and CO. Brauer and colleagues (2008) also observed elevated ORs for PTB and LBW with $PM_{2.5}$, PM_{10}, NO_2, NO, and CO but not SO_2. In Wuhan, NO_2 and CO both originate mainly from motor vehicle sources, and NO_2 and CO levels were correlated ($r = 0.66$), which may have caused the observed CO levels to conceal or distort the observable effects of NO_2. A similar pathway may exist from the observed and consistent CO effects to SO_2, causing SO_2 effects to move toward the null or become distorted, because SO_2 has the same pollution source (industrial coal combustion) as PM. SO_2 was also correlated with both $PM_{2.5}$ ($r = 0.50$) and PM_{10} ($r = 0.63$).

WEAK ASSOCIATIONS

Earlier studies have reported that, when positive associations were found, the effects of air pollution on adverse pregnancy outcomes were in general small, with ORs in the range of 1.0–1.2 per unit increase in pollutant level (Shah and Balkhair 2011). Sapkota and colleagues (2012), for example, conducted a systematic review and meta-analysis of the associations between ambient air pollution and adverse pregnancy outcomes and reported an OR of 1.02 (95% CI, 0.99–1.05) for LBW, 1.03 (95% CI, 1.00–1.06) for PTB, and 1.04 (95% CI, 1.01–1.07) for IUGR in association with a 10-μg/m^3 increase in average $PM_{2.5}$ exposure during the entire pregnancy. All reported estimates, in general, supported comparable deleterious effects of pollution on PTB, LBW, and IUGR.

Even though there were differences in the signal-to-ratio of the adverse pregnancy outcomes among the various study populations (i.e., Chinese versus non-Chinese), our estimates were comparable to those reported by the majority of previous studies and are consistent with other scientific publications on the topic (Aguilera et al. 2010; Gouveia et al. 2004; Sapkota et al. 2012). The observed weak associations are also supported by a recently published Chinese study by Zhao and colleagues (2015), who examined the relationship between PM_{10} and PTB in a birth cohort of 8969 singleton live births in the high ambient air pollution city of Lanzhou, China. They reported that a 10-μg/m^3 increase in PM_{10} during the whole pregnancy, second trimester, or 8 weeks before delivery was associated with increased ORs of 1.02 (95% CI, 0.96–1.08), 1.01 (95% CI, 0.97–1.05), and 1.01 (95% CI, 0.98–1.04), respectively. The investigators also observed significant, stronger associations for both PTB and medically induced PTB.

However, our estimates are much lower than those reported by two recently published studies from Europe and America. Pedersen and colleagues (2013) pooled data from 14 European birth cohorts to study the relationship between ambient air pollution and LBW. The primary outcome of interest was term LBW. The investigators reported an increase in risk of term LBW (OR, 1.18; 95% CI, 1.06–1.33) associated with a 5-μg/m^3 increase in $PM_{2.5}$ exposure, an OR that was much larger than our estimates. While not directly comparable, because linear regression models were used, Savitz and colleagues (2014) also reported a larger effect of ambient $PM_{2.5}$ exposure on term birth weight in New York City. We speculate that the larger effects found in these two studies may have resulted from improved exposure assessment and restriction of the study population by excluding PTBs.

Exposure misclassification might be another reason for our reported weaker associations. Using pollutant concentration data from a limited number of monitoring stations (nine in the study, of which only two measured $PM_{2.5}$) near the center of the study participants' community of residence as proxies for personal exposure data assumes that pollution levels were homogeneous across the study

areas. In addition, personal measurements of ultrafine particles, PAHs, and other traffic constituents were not available. There would be significant exposure uncertainty if large local pollution sources existed, such as traffic emissions or construction. This possible misclassification would occur approximately equally between study groups, thus increasing the similarity of the study groups and biasing the relative risk for any true exposure–disease association toward the null (van den Hooven et al. 2012). Furthermore, PTB, LBW, or IUGR have a variety of etiologies and pathogeneses, and heterogeneity of risk factors could cause a single adverse pregnancy outcome. Among all hypothesized risk factors for adverse pregnancy outcomes, air pollution ought to be considered a small risk factor (Institute of Medicine 2009; Behrman and Butler 2007). The difference in this small risk factor would increase "noise" and decrease signal-to-ratio for the effects from air pollution, which could be another potential reason for our reported weak associations (Shah and Balkhair 2011).

NEGATIVE OR ABSENT ASSOCIATIONS

Associations between exposure to air pollutants and adverse pregnancy outcomes have varied by study. Reported negative or absent associations are not uncommon (Fleischer et al. 2014; Gehring et al. 2011b). We, too, observed a few equivocal and small negative associations, especially for SO_2 and NO_2. To date, we have identified more than 10 previous studies that reported negative associations (Aguilera et al. 2010; Fleischer et al. 2014; Geer et al. 2012; Laurent et al. 2013; Slama et al. 2007). Negative or absent associations have been found in areas with both high and low pollution levels (Mannes et al. 2005). Fleischer and colleagues (2014), for example, reported that $PM_{2.5}$ was not associated with PTB. Laurent and colleagues (2013) observed positive associations between LBW and O_3 but negative or absent associations between LBW and $PM_{2.5}$, PM_{10}, NO_2, NO, NO_x, and CO. Brauer and colleagues (2008) identified no association between O_3 and IUGR. Gehring and colleagues (2011a,b) observed nonsignificant associations between exposure to traffic-related pollutants ($PM_{2.5}$ and NO_2) and PTB and LBW. Wilhelm and colleagues (2012) observed no associations between $PM_{2.5}$ or CO exposure and LBW over the entire pregnancy. Malmgvist and colleagues (2011) suggested that exposure to low levels of air pollutants in Scania, Sweden, might be associated with protective effects on PTB. Similar findings were also reported by Slama and colleagues (2007) and Aguilera and colleagues (2009). No association was observed for weekly or daily levels of PM_{10} in Shanghai, China (Jiang et al. 2007). Chang and colleagues (2012) also observed a nonsignificant association between short-term exposure to $PM_{2.5}$ and PTB in North Carolina.

Four previous Chinese studies have reported positive associations between SO_2 concentrations and adverse pregnancy outcomes. Two of these studies used a community-based cohort in Beijing, China, about 20 years ago (Wang et al. 1997; Xu et al. 1995). At that time, coal was the principal combustion source in China, with high household use; today no household in Wuhan uses coal. Higher concentrations of SO_2 existed in Beijing at that time (mean = 102.0 $\mu g/m^3$) than in the current study of Wuhan (mean = 35.8 $\mu g/m^3$). The difference in SO_2 pollution levels may be the reason for the difference in the observed health effects of SO_2. The other two, more recent Chinese studies used a time series design and reported short-term effects of SO_2 on PTB in Guangzhou (Zhao et al. 2011) and Shanghai (Jiang et al. 2007). However, other studies have found nonsignificant results (Landgren 1996).

The contrast in results could also have been caused by differences in exposure assessment (i.e., exposure uncertainty and colinearity of pollutants), populations, and study design. Spatial and temporal heterogeneity of the pollutant species may explain the reported inconsistencies (Kumar 2012). Bell and colleagues (2010), for example, found effect differences for birth weight with various constituents of $PM_{2.5}$ in a study based in Connecticut and Massachusetts and concluded that the differences in the composition and source of PM would contribute to differences in results across studies. Geer and colleagues (2012) also reported that effect differences in birth weight by region in Texas might have been partially attributable to differences in air pollution mixtures, particularly with respect to the differing chemical structures of the particles. Another reason for the observed equivocal and negative associations could have been the use of data from a limited number of monitoring stations. Reduced variability in exposure to air pollution may be another possible explanation for the absent associations in our study (Tables M.2–M.10 in Appendix M; Gehring et al. 2011b). Our monitoring stations were all located in urban areas. These homogeneous locations probably contributed to the unrealistically high correlations between pollutants and could have limited their spatial variability. (The air monitoring stations were, of course, originally sited for policy and regulation purposes, not for environmental health research.) The measurements of the study pollutants at these stations consequently might not be ideal for air pollution epidemiological studies (Woodruff et al. 2009). In addition, our analyses included fitting many regression models. The observed equivocal and negative associations might have

been caused by pure chance (a 5% type I error). Furthermore, increasing evidence has shown that endocrine disruptor compounds are associated with obesity (Rundle et al. 2012). However, we are not aware of any proposed biological mechanisms whereby endocrine disruptors increase birth weight. Lastly, we did not collect data on fetal deaths or early miscarriages. The full continuum of adverse pregnancy outcomes would include these pregnancy losses as well as PTB, LBW, and IUGR. If exposure to a specific pollutant triggers pregnancy loss, the remaining pregnancies that yield a live birth could show an increased average birth weight when compared with those without the exposure and therefore a falsely negative association with that pollutant.

SUSCEPTIBLE EXPOSURE WINDOWS

Debate has been ongoing as to the susceptible exposure windows during pregnancy. Inconsistent results exist (Aguilera et al. 2009; Bell et al. 2010; Lacasana et al. 2005; Rich et al. 2009; Ritz and Wilhelm 2008; Slama et al. 2007). Brauer and colleagues (2008), for example, concluded that inconsistent patterns existed for the most susceptible exposure window and that high correlations between exposures in individual trimesters and exposures over the entire pregnancy would make it more difficult to identify the most susceptible exposure window for a given pollutant. Two recent systematic reviews and meta-analyses, conducted by Stieb and colleagues (2012) and Shah and Balkhair (2011), also identified these inconsistencies. For CO, 17 studies were identified that examined the association between CO exposure and adverse pregnancy outcomes. Increased risks for LBW were reported by two studies for exposure in the third trimester (Maisonet et al. 2001; Ritz and Yu 1999). However, higher risks in the first and second trimesters, but a lower risk in the third trimester, were reported in another study (Lee et al. 2002). Another study reported no association between CO concentrations and LBW (Laurent et al. 2013). Liu and colleagues (2003) reported that PTB was positively associated with CO concentrations in the last month of pregnancy, and a similar relationship was observed between small for gestational age (SGA) and CO concentrations in the first month of pregnancy. Shah and Balkhair (2011) identified eight studies in which $PM_{2.5}$ effects on adverse pregnancy outcomes had been examined. Huynh and colleagues (2006) found a positive association between LBW and $PM_{2.5}$ concentrations during the entire pregnancy, particularly in the last 2 weeks of pregnancy and the first month of pregnancy. Similar positive associations were reported by two studies for PTB (Ritz et al. 2007) or SGA (Parker et al. 2005). However, two other studies reported no associations for SGA (Madsen et al. 2010; Mannes et al. 2005).

We explored critical exposure windows and metrics that influenced adverse pregnancy outcomes for each pollutant in our study. We recognize, however, that this task was challenging, because a mother's exposures are likely to be highly correlated in the various trimesters across the pregnancy. We were unable to consistently identify critical exposure windows for any pollutant in the study. Overall, our effect estimates were the same for many pollutants in the various trimesters. When the estimates did differ across trimesters, the majority of differences were very small (the largest effects in the second trimester were for $PM_{2.5}$, PM_{10}, SO_2, O_3, and CO). We speculate that these observations may have resulted from the moderate to high correlations among the exposures in the trimesters across the pregnancy (see Table 2 and Tables M.11 and M.12 in Appendix M) and that the correlations may have inhibited our effort to tease out independent health effects in the various exposure windows.

While our findings seem plausible, exposures during the first trimester, third trimester, and last weeks before delivery have been identified as having the most relevance for both LBW and PTB (Ritz and Wilhelm 2008). Fetal implantation could be affected by pollutant exposure during the first weeks, and fetal growth could be affected by exposure in the third trimester, when fetal weight gain is most rapid (Gouveia et al. 2004). Large health effects in the first trimester may indicate that pollutants have an effect on placental development and on maintenance of the pregnancy, because stress in the first trimester is most likely to trigger events that lead to a subsequent PTB; and large effects in later pregnancy may be caused by pollutants affecting maternal and placental vascular function, which can in turn cause IUGR (Mannes et al. 2005). Lee and colleagues (2013) reported that first-trimester exposure to $PM_{2.5}$ and O_3 were associated with increases in the risk of PTB, SGA, preeclampsia, and gestational hypertension. Huynh and colleagues (2006) reported larger effects from $PM_{2.5}$ exposure for the first month and last 2 weeks of pregnancy. Larger first-trimester effects were also reported for LBW and SO_2 (Bell et al. 2007; Liu et al. 2003; Mohorovic 2004). Larger third-trimester effects were reported for $PM_{2.5}$ exposure on LBW in New York City by Savitz and colleagues (2014) and for O_3 exposure on IUGR and LBW in North Carolina by Vinikoor-Imler and colleagues (2014). However, Salam and colleagues (2005) and Geer and colleagues (2012) observed larger effects of O_3 during the second trimester. These findings were supported by van den Hooven and colleagues (2012),

who provided evidence that air pollution exposure could affect fetal growth from the second trimester onward.

Interpretation of the differences in these results requires caution. First, the inconsistencies might relate to differences in the study designs or study cities. In addition, misclassification of the exposure may exist for different gestation periods, because the majority of previous studies used birth certificate data and determined gestational exposure based on the date of the LMP reported on the birth certificate. An inaccurate gestational age at birth might have been reported, given that LMP yields an approximate date (Bell et al. 2007). Sapkota and colleagues (2012) reported that using LMP would more likely lead to exposure misclassification for the first two trimesters of pregnancy, making exposure estimates more similar between exposure groups. This misclassification would lead to effect estimation toward the null (Geer et al. 2012). Furthermore, estimated exposures during different pregnancy periods are in general correlated with each other and with exposures during the entire pregnancy (Appendix O). These correlations may have limited our ability to tease out the health effects of exposures during specific pregnancy windows, as we had originally proposed (Brauer et al. 2008; Wilhelm et al. 2012). However, our sensitivity analyses were extended to analyses that included all three time windows. The results showed that there were no changes in the estimated associations or that the changes were very small, indicating that our estimated effects were stable (Tables M.46–M.48 in Appendix M). While most of the previous studies and ours have been limited to providing such evidence, because of the high correlations, this gap in the knowledge base warrants further research (Chang et al. 2012). Lastly, exposures during the entire pregnancy resulted, in general, in the most robust estimated effects. In the current report, therefore, we focused on the health effects of exposures during the entire pregnancy.

EFFECT MODIFICATIONS BY TEMPERATURE EXTREMES, SES, AND SHS EXPOSURE

Temperature-Modified Associations

The health effects of temperature extremes on adverse pregnancy outcomes have been reported previously, but results have been inconsistent (Auger et al. 2014; Lawlor et al. 2005; Schifano et al. 2013). Lawlor and colleagues (2005) reported that higher ambient temperatures around the time of conception were associated with decreased birth weight, using data from children in the 1950s Aberdeen (Scotland) cohort. It is worth noting the differences between the Aberdeen study and the current study. In the Aberdeen study, the temperatures in the warmest fifth of the range were from 9.0°C to 17.6°C. In our study, they were 31.6°C and above. A recent study in Rome was designed to examine independent effects of exposure to ambient temperatures and PM_{10} on PTB and reported short-term effects from heat (Schifano et al. 2013). However, Wolf and Armstrong (2012) did not find positive associations between temperature exposure during various pregnancy periods and LBW or PTB.

Few studies have investigated the interactions between exposure to temperature extremes and air pollution on adverse pregnancy outcomes, and the mechanism of possible interaction effects is unknown (Dadvand et al. 2014; Kent et al. 2014). One major reason is that examining the interaction effects is a difficult undertaking in most cases, because a suitable study site with both high pollution levels and temperature extremes is not readily available. The study city of Wuhan provided an opportunity to examine these effects.

No clear patterns were observed for the modification of temperature extremes, although larger effects were observed on both low or high temperature days. The strongest effect of $PM_{2.5}$ on PTB, for example, was found on high temperature days. These observations are similar to those of a previous study of ours in Wuhan, which indicated that high temperature increased PM_{10} effects on daily non-accidental, cardiovascular, and cardiopulmonary mortality (Qian et al. 2008a). The presence of temperature extremes, high pollution levels, and wide pollution ranges may be related to the observed interaction effects. Historically, Wuhan has been called an "oven" city because of its extremely hot summers. The maximum temperature in summers often exceeds 40°C and may continue for 2 weeks. In winters, Wuhan's coldest temperatures are often below 0°C. In addition, we observed high daily pollutant concentrations and wide pollution ranges for all pollutants of interest (Qian et al. 2001).

The mechanism underlying the interaction effects is not clear. Some potential explanations have been posited, including the possibility that physiological functions require the maintenance of relatively constant body temperature and that humans suffer morbidity more easily at temperature extremes (Donaldson et al. 1998; Klinenberg 2003; Lawlor et al. 2005). Animals subjected to heat stress during pregnancy tend to produce LBW offspring (Galan et al. 1999). Wells (2002) proposed that heat waves in early pregnancy might result in poor placental growth and subsequent IUGR. Lawlor and colleagues (2005) proposed that temperature extremes during gestation might be related to changes in women's behaviors and time–activity patterns. Such changes may be the mechanism linking temperature extremes to adverse pregnancy outcomes. Cold temperatures may hinder normal growth, and high temperatures

would lead to reduced body size because of the adaptation to heat through a higher surface-to-volume ratio (Speakman and Król 2010; Wells 2002; Wolf and Armstrong 2012). Cold exposure is thought to more plausibly hinder normal growth (Murray et al. 2000).

SES

Air pollutants may lead to strong effects among the socioeconomically disadvantaged (Luo et al. 2006). Subramanian and colleagues (2006) showed that adverse pregnancy outcomes were associated with lower SES. Recently, more studies have examined the role of SES in the vulnerability of subpopulations to air pollution (Gray et al. 2013), but inconsistent findings have been reported (Gouveia and Fletcher 2000; Kan et al. 2008; Parker et al. 1994). Gray and colleagues (2014) observed that more socially disadvantaged populations are at a greater risk from air pollution. Another study, in Shanghai, China, reported that lower SES might be a risk factor for air pollution–mortality effects (Kan et al. 2008). In contrast, an earlier study of ours, in four Chinese cities, showed a larger effect from air pollution among children with higher parental SES (Qian et al. 2007a). Gouveia and Fletcher (2000) reported similar results, finding larger effects of pollution in areas of higher SES. No differentiated susceptibility to air pollution by SES was reported by Bateson and Schwartz (2004).

Maternal education is related to other SES measures and has commonly been used in perinatal studies (Parker et al. 2011; Pickett et al. 2002). Interactions among education levels, air pollution, and adverse pregnancy outcomes also remain inconsistent. While mothers with lower education generally have poorer outcomes, the magnitudes of the effects depend on the outcome in question (Parker et al. 1994). Mothers with higher education were reported to live in low pollution areas in previous studies (Woodruff et al. 2003), but other studies have reported that the high education mothers could also live in high pollution areas (Qian et al. 2004).

Several pathways may exist for household income to modify air pollution effects on adverse pregnancy outcomes, though the reasons for not seeing a clear interaction pattern are unknown. First, women with lower household income may be more sensitive to air pollution because they are more likely to have preexisting diseases that confer a greater risk of adverse pregnancy outcomes associated with air pollution. Second, because women with lower household income may have reduced access to healthy food such as fish and vegetables, they might have a more limited intake of protein or antioxidant polyunsaturated fatty acids and vitamins that may protect against adverse pregnancy outcomes (Romieu et al. 2008). Disadvantaged living conditions may also play an important role in affecting adverse pregnancy outcomes. Women with lower household income may be less likely to have air conditioning and therefore to have higher pollution exposure because of poor housing in spite of identical concentration measurements at monitors (Qian et al. 2001).

SHS Exposure

The effects of household air quality have not been well documented (Pope et al. 2010) even though pregnant women spend the majority of time indoors. While we found larger effects from $PM_{2.5}$ and O_3 on PTB in women exposed to SHS than in non-exposed women, no clear interaction patterns were observed. The lack of effects from SHS exposure has been reported in other published literature in China (Qian et al. 2000). Our previous studies in Wuhan also observed that the fathers' smoking status was not associated with forced vital capacity or forced expiratory volume at 1 second among schoolchildren (Qian et al. 2007a). We offer two interpretations for this observation. Our previous studies in the city showed that approximately 80% of the fathers were smokers (Qian et al. 2004a). The wives of the 20% of fathers who did not smoke were most probably exposed to significant SHS in public or at work, because no law or administrative policy actually inhibits cigarette smoking in public in Wuhan, and a high proportion of men smoke. Hence SHS exposure occurs during most social activities or events. The contrast in SHS exposure between women whose husband did and did not smoke would thus be diminished.

STRENGTHS

The current study has several major strengths.

First, it was a population-based prospective cohort study within which a large case–control study was constructed. All eligible births occurring during the study period in the seven urban core districts of Wuhan were recruited. Selection bias was thus unlikely.

Second, to our knowledge, this was the first study of effects from air pollution on adverse pregnancy outcomes in China using a prospective cohort study design. Because of this design and the large sample size, we were able to evaluate effect modification by temperature extremes, maternal educational attainment, household income, and SHS exposure. Evidence provided from the study has shed light on the most susceptible populations of pregnant women, allowing more targeted interventions in the future.

Third, the study population was recruited from a single large metropolitan area, decreasing variability in many unmeasured and unknown risk factors and increasing the study's statistical power. For example, all residents and participants received their prenatal care from the same

maternal and child health care system, and consistent procedures and standardized protocols were used in the data collection. Although the identified effects were small per unit change in pollutants and the adverse pregnancy outcomes occurred at relatively low prevalence in Wuhan compared with those of the United States (e.g., PTB was 4.5% in the study population compared with 12.5% in the United States), the public health impact would be considerable because of the ubiquitous exposure to high levels of air pollutants across an entire population.

Fourth, earlier studies have reported change-of-residence or mobility rates for pregnant women in the United States as ranging from 9% to 35%; of these, 4% to 7% move locally (Lupo et al. 2010; Madsen et al. 2010). No data on mobility during pregnancy has been reported for Chinese pregnant women. The mobility rate during pregnancy in the current study was 8.4% for the 7409 cases and controls, lower than those reported from the U.S. studies. This observation is consistent with our experience working in the study communities. Pregnant women have been less likely to move during their pregnancy compared with non-pregnant women. As reported in the data source section, pregnant women in Wuhan are required to register at their district's maternal health care center and receive regular care at their community maternal child health center within 3 months of becoming pregnant. After delivery, mothers are required to visit the community maternal and child health care centers for postnatal and pediatric care. This comprehensive district-based perinatal health care system encourages very low residential mobility for pregnant women. In addition, adjusting for residential mobility in our study resulted in no appreciable changes in the estimated effects; neither did re-analyzing the data when including only the non-movers in the case–control study. These findings are in line with results reported by Pereira and colleagues (2016) that accounting for residential mobility during pregnancy had negligible benefits. Furthermore, van den Hooven and colleagues (2012) reported that such possible exposure misclassification is more likely to be nondifferential, thus leading effect estimates toward the null.

Lastly, we obtained a response rate of 63.2% in the survey for the nested case–control study. Previous similar studies reported response rates of less than 55% (Llop et al. 2010; Ritz et al. 2007). The increased participation in the current study helps reduce concerns about potential selection bias and response bias.

LIMITATIONS

Despite these strengths, our results should be interpreted in light of several limitations.

First, a major limitation was that only data for outdoor $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO levels were available. There were no simultaneous measurements of indoor air pollution, and we had to rely on self-reporting for information about indoor sources, such as household cigarette smoking. If the indoor pollution levels differed substantially from the outdoor levels, lack of control for the indoor levels in our analysis of the outdoor air pollution could diminish the power to detect significant effects. However, our previous studies in the same city showed that using self-reported indoor pollution source data was an effective way to control for such confounding (Qian et al. 2007a).

Second, we did not collect exposure data for nonresidential locations, such as work sites. Previous studies have shown that pregnant women who spent more time indoors than outdoors might experience stronger effects on adverse pregnancy outcomes (Aguilera et al. 2010; Nethery et al. 2008). However, the estimated effects of outdoor air pollution on adverse pregnancy outcomes are likely to be free of confounding by indoor pollution at nonresidential locations, because such pollution is expected to be independent of the residential pollution levels. In addition, our study collected information on maternal occupation by way of a questionnaire. This information was used to develop surrogates for occupational exposures, which were controlled for in the data analyses. Furthermore, we adjusted for maternal education and household income, which would be related to maternal occupation. The study was thus able, at least partially, to remove such confounding. Although we controlled for the number of hours spent indoors for pregnant women, no data were available on the amounts of time spent in other microenvironments where exposures might have occurred. Exposure uncertainty remains (Nethery et al. 2009), which may in turn have affected the accuracy of our effect estimates.

Third, exposure misclassification may be present in the study. The study was carried out during a peak period of construction in Wuhan, when there were 11,012 active construction sites throughout the city, including the construction of subways and multiple-story buildings. Unfortunately, we did not have any data about the exact locations of all of these local pollution sources. The construction sites were usually correlated with major roads or subway entrances or exits. We were limited in our efforts to tease out the effects of exposure to major roads versus the construction sites, though we did control for major roads as an important covariate.

Multiple high-density roads surrounded most participants' residences in the seven urban core districts. We considered only one major road. Data on the traffic density of other roadways were not available. This is an important

limitation, because in urban areas, traffic even on smaller roads might be dense enough to produce pollution levels similar to those of a single major road (Miranda et al. 2013). In addition, we did not collect data on traffic counts, types of traffic on roads, or seasonal variations in traffic. We did control for road proximity in our analyses and found that it was not a confounder. The reasoning behind our decision to consider only one major road was that most of the participants lived in urban core districts with highly traveled roadways, which would make locally elevated air pollution levels related to road proximity well mixed. This mixing of pollution levels would increase the similarity of exposures and move relative risk estimates toward the null. Although we recognized that road proximity may be associated with both noise exposure and pollutant exposure, we could not tease out its effects in this study.

Another possible source of exposure misclassification is that we estimated exposures based on residential communities at the time of the index birth. Like most of the previous studies, we relied on pollutant concentrations measured from a limited number of routine air monitoring stations in the study area. The monitoring stations were limited in spatial resolution and could not capture the spatial heterogeneity of pollutants emitted from local pollution sources (Yorifuji et al. 2011). Our study was thus limited in its ability to disentangle the relative impacts of local, regional, and background pollutants. However, the average area of the communities was approximately 2 km^2, and the inability to address spatial heterogeneity of pollutants within a community may be particularly important for larger communities (Peng and Bell 2010). Exposure misclassification may be significantly greater for residents living far away from monitors. In our study, the maximum distance between a monitoring station and a central point in the community where a participant lived was 17.3 km. Such a distance may lead to a considerable measurement error, especially when significant local pollution sources exist. This misclassification should occur approximately equally among study groups, thus increasing the similarity among the groups and biasing the relative risk for any true exposure–disease association toward the null. In addition, exposure data on ultrafine particles, PAHs, and other traffic constituents were not available. Thus, the observed associations should be interpreted with consideration for this limitation (Gehring et al. 2014; Shah and Balkhair 2011).

Fourth, we defined PTB as based on reported LMP, which may have been an approximate date. Measurement errors in estimating gestational age could be differential (Zeger 2012). This approach could have systematically overstated the duration of gestation (Savitz et al. 2002), which would lead to an underestimation of PTB. However, Dietz and colleagues (2007) compared gestational ages estimated from LMPs with gestational ages estimated from first-trimester ultrasounds and obtained similar results for both methods (8.7% of PTB from LMP and 7.9% from ultrasound). We conducted a substudy of our own to compare gestational ages estimated from LMPs with estimates from first-trimester ultrasounds and also obtained similar results (Table 12). We defined IUGR as a weight below the 10th percentile for gestational age based on the total cohort sample. This definition is controversial, because it doesn't distinguish among fetuses with restricted growth who were small, fetuses with restricted growth who were not small, and fetuses who were constitutionally small (Brauer et al. 2008). However, the definition is commonly used in the study field and facilitates comparisons among studies.

Fifth, most of the pollutants were moderately or highly correlated (as shown in Table 2 and Appendix O), as reported in many previous studies (Huynh et al. 2006; Sarnat et al. 2005). These correlations occurred between pollutants within a pregnancy period as well as between different pregnancy periods (trimesters and months). High colinearity made it challenging to compare the relative health effects of the study pollutants in different pregnancy periods and impossible to tease out the effects of single pollutants on the adverse pregnancy outcomes (Brauer et al. 2008; Shah and Balkhair 2011).

Lastly, while our sensitivity analyses showed that the results from the logistic regressions were in general comparable to those from the linear regressions, discrepancies in the estimated effects existed for some pollutants. Linear regression analyses would lead to inconsistent effect estimations if the relationship between the exposure and outcomes were not linear. This warrants exploration of the complicated exposure–response curves to determine the precise relationships between the exposures and the adverse pregnancy outcomes.

CONCLUSIONS

Our study adds to the known evidence about the adverse effects of ambient air pollution exposure on pregnancy outcomes. The study's key findings include the following:

- Exposures to ambient $PM_{2.5}$, PM_{10}, CO, and O_3 were positively associated with PTB. The associations for SO_2 and NO_2 were negative.
- Relatively weak evidence of positive associations was observed between the pollutants and both LBW and IUGR.
- The majority of estimated effects from the two-pollutant models were similar to those estimated from the single-pollutant models.

- The observed associations with adverse pregnancy outcomes appeared not to be biased by residual confounding, as evidenced by controlling for covariates collected at delivery.
- No consistent critical exposure windows were identified.
- Temperature extremes at conception might modify the effects from $PM_{2.5}$, SO_2, CO, and O_3 on both PTB and LBW. Further studies are needed to confirm these observations.
- No clear interaction patterns were observed for maternal educational attainment, household income, or SHS exposure.

IMPLICATIONS OF FINDINGS

Our study adds to the body of evidence about air pollution and adverse pregnancy outcomes — a research need documented by both Chinese and American regulatory agencies, including the U.S. EPA. It is one of a few studies to date and the first in China to use a prospective longitudinal cohort and nested case–control sample for examining effects of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO on adverse pregnancy outcomes.

The study, which was conducted in the "oven" city of Wuhan, China — where high air pollution levels, wide pollution ranges, and extremely high summer temperatures exist — provides new information about the effects of air pollution on pregnancy outcomes. Findings from the study provide important international scientific context for U.S. studies of air pollutants (which have been limited by lower pollutant levels) and enable assessment of the plausibility of the U.S. findings. The study also observed adverse effects that could be prevented by both U.S. and Chinese environmental regulations. In addition, identifying susceptible populations and determining significant interaction effects of air pollution and temperature extremes have implications for both scientists and relevant governments in efforts to protect public health through the regulation of air pollution.

If they are confirmed, the interaction effects of air pollution and temperature extremes on both PTB and LBW observed in this study deserve particular attention because of the fact that both high summer temperatures and high levels of air pollution can often occur in large metropolitan areas. Large cities like Wuhan are likely to experience increases in the incidence of heat-and-pollution-related health effects during periods of high heat. There is therefore a need for relevant governmental bodies to take a preventive approach by cutting emissions, which is expected to substantially reduce both high urban temperatures and air pollution, including greenhouse gases. Reducing fossil fuel combustion would also have significant direct health benefits by preventing many heat- and pollution-induced adverse pregnancy outcomes. The identified susceptible populations have implications for Chinese local and national governmental efforts to protect public health through the regulation of air pollution.

The consistency of the observed ORs gives us confidence that synthesizing effect estimates of the associations between air pollutants and adverse pregnancy outcomes reported by studies with different populations, exposure, study designs, or research approaches is informative. This consistency reinforces the need for exposure reduction, especially for pregnant women and their children. Pregnant women should be encouraged to pay more attention to local air quality and adjust their time–activity patterns — by, for example, limiting the duration of time spent outside on roads when air pollution levels are high. Findings from this study could also be important for policy makers in applying research evidence to policy, such as inclusion of our estimated effects in future revisions of air quality standards.

FUTURE RESEARCH

Three directions for further research are within reach, as briefly outlined below:

First, like most of the previous studies, our study assumed a linear relationship between air pollution and adverse pregnancy outcomes. Yet there is insufficient evidence about the actual shape of the exposure–response relationships. We analyzed the data by tertiles (i.e., the top, middle, and bottom thirds of each pollutant level). While the results were similar to those for the associations in the main data analysis, the meaning of the results is still unclear — and we are unsure if the relationships are in fact linear. We may have been pushing the data by dividing the whole study population into groups or by making assumptions that variables were all normally distributed. We speculate that the relationships between the adverse pregnancy outcomes and some of the pollutants (e.g., SO_2 and NO_2) may not be linear. If our speculation is true, the results obtained from the study make sense: We observed different estimated ORs in terms of magnitude, direction, and 95% CIs among the exposure groups. Positive associations or the largest ORs were found only in the highest exposure groups for PTB with $PM_{2.5}$, PM_{10}, CO, and O_3 as well as for LBW with $PM_{2.5}$, PM_{10}, and CO. The ORs in the medium exposure groups for some pollutants (e.g., CO and PM_{10})

were actually smaller than 1, which was the OR in the lowest exposure groups. These results indicate that the relationships may not be linear. A recent study by Savitz and colleagues (2014) also found different shapes for the relationships among high, medium, and low exposure groups in New York City by using penalized spline models for each exposure window. Much more comprehensive effort, similar to that undertaken by Savitz and colleagues (2014), would be needed to address this challenging question. Exploring the shapes of the relationships was out of the scope of this study, but we plan to explore such shapes in the near future.

In addition, our study estimated exposure to air pollutants using concentrations measured only from nine monitoring stations. This method is limited to addressing gradients in exposure between different urban sectors and does not account for local variations in air pollution levels. Reduced variability in exposure may be one of the reasons for the observed small associations. More recent approaches are able to consider finer spatial and temporal contrasts in exposure (Aguilera et al. 2010; Ballester et al. 2010; Gehring et al. 2011a). We plan to use a spatiotemporal exposure model based on land-use regression and a temporal component from air monitoring data to assess participant exposures. This approach could reduce exposure uncertainty and is expected to generate improved exposure estimates.

Lastly, global warming is projected to increase ambient temperatures. Epidemiological studies allow us to further identify how thermal stresses cause increased adverse pregnancy outcomes, as well as how important factors such as air pollution and poverty modify the associations between thermal stress and adverse pregnancy outcomes. Determining the main effects of heat waves on adverse pregnancy outcomes and related effect modifiers are clearly our next steps.

ACKNOWLEDGMENTS

This work was conducted under contract to HEI and was made possible in part through support provided by Saint Louis University, Wuhan Medical and Health Center for Women and Children, and the WEMC. The investigators are thankful for the useful comments and advice offered by HEI's International Scientific Oversight Panel. We are also grateful to Drs. Michael Elliott, Beate Ritz, Jun Wu, Jason Su, Carol S. Weisman, and Katherine J. Hoggatt for their constructive comments.

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HEI QUALITY ASSURANCE STATEMENT

The conduct of this study was subjected to independent audits by Mr. David Bush of T&B Systems, Inc. Mr. Bush is an expert in quality assurance for air quality monitoring studies and data management. The audits included on-site reviews of study activities for conformance to the study protocol and operating procedures, and selected performance audits of monitoring equipment. The dates of the audits are listed below, along with the phase of the study examined.

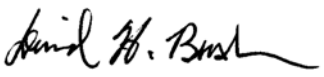
October 15–17, 2012

The auditors conducted on-site audits at several study-related facilities in Wuhan, China, including the Wuhan Medical and Health Center for Women and Children and the Wuhan Environmental Monitoring Center. Dr. Haidong Kan participated in this audit, providing expertise for the review of the clinical portions of the study. The audit included a review of data collection procedures at regional and community data collection facilities for both air quality and clinical data. No significant issues were noted.

April 18–20, 2016

The auditor reviewed the study final report, as well as the final data set used in the analysis, during an on-site visit to Saint Louis University. Several data points were traced through the data management sequence to verify the integrity of the data set, though the residence of the raw data and quality control data in China prevented a thorough review of quality control activities. The reproducibility of statistical analyses results was also confirmed during the audit. No significant issues were noted.

Written reports of each inspection were provided to the HEI project manager, who transmitted the findings to the principal investigator. These quality assurance audits demonstrated that the study was conducted by an experienced team with a high concern for the quality of the collected data. The report appears to be an accurate representation of the study.



David H. Bush, Quality Assurance Officer

MATERIALS AVAILABLE ON THE WEB

Additional Materials contains Appendices A through P, which are supplemental materials not included in the printed report. They are available on the HEI Web site *www.healtheffects.org/publications.*

Appendix A. Data Sources

Appendix B. Standard Operating Procedures for Air Pollution Data Collection

Appendix C. Procedures for Estimating Exposure Using the Closest Monitor Approach

Appendix D. Procedures for Estimating Exposure Using the Inverse-Distance Weighting Approach

Appendix E. Standard Operating Procedures for Pregnancy Outcome Collection

Appendix F. Questionnaire

Appendix G. Data Management, Quality Assurance, Quality Control, and Data Integrity and Security

Appendix H. Data Structure and Codebook for Delivery Data

Appendix I. Data Structure and Codebook for the First Prenatal Care Visit Data

Appendix J. Data Structure and Codebook for Questionnaire Data

Appendix K. Power Calculation

Appendix L. Two-Phase Data Analyses

Appendix M. Additional Results of Aim 1

Appendix N. Additional Results of Aim 2

Appendix O. Additional Results of Aim 3

Appendix P. Additional Results of Aim 4

ABOUT THE AUTHORS

Zhengmin Qian, M.D., Ph.D., is a professor and chair of the Department of Epidemiology at Saint Louis University College for Public Health and Social Justice, Saint Louis, Missouri, USA. From 1987 to 2001 he was a key investigator on the U.S. Environmental Protection Agency–sponsored study "Health Effects of Long-Term Air Pollution on Lung Function and Respiratory Health in Children and Adults in Four Chinese Cities" under annex 1 of the China–U.S. Protocol for Scientific and Technical Cooperation in the Field of Environment Protection. From 2004 to 2007 he was the principal investigator for the study "Association of Daily Mortality with Ambient Air Pollution, and Effect Modification by Extremely High Temperature in Wuhan, China" (in Research Report 154), sponsored by HEI. His research areas of focus include maternal and child health,

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OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Qian Z, Liang S, Yang S, Trevathan E, Huang Z, Yang R, et al. 2015. Ambient air pollution and preterm birth: a prospective birth cohort study in Wuhan China. Int J Hyg Environ Health 219:195–302; doi:10.1016/j.ijheh.2015.11.003.

ABBREVIATIONS AND OTHER TERMS

aOR	adjusted OR
CI	confidence interval
CO	carbon monoxide
EPA	Environmental Protection Agency
IDW	inverse distance weighted
IR	Investigators' Report
IUGR	intrauterine growth retardation
LBW	low birth weight
LMP	last menstrual period
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O_3	ozone
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
PAPA	Public Health and Air Pollution in Asia
PM	particulate matter
$PM_{2.5}$	particulate matter ≤2.5 μm in aerodynamic diameter
PM_{10}	particulate matter ≤10 μm in aerodynamic diameter
PTB	preterm birth
SD	standard deviation
SES	socioeconomic status
SHS	secondhand smoke
SGA	small for gestational age
SO_2	sulfur dioxide
WEMC	Wuhan Environmental Monitoring Center

CRITIQUE

Health Review Committee

Research Report 189, *Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China*, Z. Qian et al.

INTRODUCTION AND BACKGROUND

Dr. Zhengmin Qian's study, "Ambient Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China," was funded under HEI Request for Applications 09-2, "Impact of Air Pollution on Infant and Children's Health in Asia." It was intended to further HEI's Public Health and Air Pollution in Asia (PAPA*) program to help bring an international perspective to HEI's work and to advance scientific knowledge about the health effects of air pollution in Asia and around the world.

Several recent studies have suggested that maternal exposures to air pollution and temperature extremes might contribute to low birth weight (LBW), preterm birth (PTB), and other outcomes that can adversely affect infant health (see, for example, reviews of this literature by Amegah et al. 2014; Dadvand et al. 2013; Lai et al. 2013; Lamichhane et al. 2015; Parker et al. 2011; Stieb et al. 2012). At the time the current study began, most other studies had been conducted in the United States or Europe. Qian proposed to extend earlier work he had done on ambient particle air pollution and daily mortality in Wuhan, China (Qian et al. 2010), as part of the PAPA program, to investigate associations between air pollution and adverse pregnancy outcomes. Wuhan is the capital city of Hubei province in central China and has a population of about 10 million people, of which about 6.4 million live in the seven inner-city districts which comprise the study area for this project.

Specifically, he proposed a cohort and nested case–control study design to evaluate whether high ambient levels of particulate matter (PM) with a mass median aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) and 10 μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), or carbon monoxide (CO) were associated with increased occurrences of PTB, LBW, or intrauterine growth retardation (IUGR) in a cohort of neonates born in Wuhan during a 2-year period (June 2011 to June 2013).

With this work, Qian and colleagues hoped to address limitations they had identified in earlier studies. They noted that air pollution levels in Wuhan, which are generally much higher than those observed in the United States and Europe, would provide a stronger basis for exploring the relation between air pollution and adverse pregnancy outcomes, including the effects of individual air pollutants independent of others. Given the large population, the investigators also anticipated being able to explore the importance of different time windows of exposure. In addition, because Wuhan experiences high temperatures in summer (the Investigators' Report [IR] stated that "the average daily maximum temperature in July is 37.2°C and that the maximum daily temperature often exceeds 40°C") and cold winters with frequent freezing temperatures, the investigators planned to examine potential modifications of the air pollution effects by temperature. With the nested case–control study, they planned to collect individual data on a number of factors that might confound or modify the impact of air pollution on the adverse pregnancy outcomes.

This Critique provides the HEI Health Review Committee's evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the IR into scientific and regulatory perspective.

Dr. Qian's 3-year study, "Air Pollution and Adverse Pregnancy Outcomes in Wuhan, China," began in November 2010. Total expenditures were $304,164. The draft Investigators' Report from Qian and colleagues was received for review in August 2014. A revised report, received in April 2015, was provisionally accepted for publication in June 2015 pending further revisions. A second revision of the report, received in September 2015, was accepted for publication in October 2015. During the review process, the HEI Health Review Committee and the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Critique.

This document has not been reviewed by public or private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views of these parties, and no endorsements by them should be inferred.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

DESCRIPTION OF THE STUDY

SPECIFIC AIMS

The investigators outlined four specific aims:

1. To evaluate whether levels of exposure to air pollutants (specifically $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3, and CO) during vulnerable pregnancy periods were associated with increased rates of PTB, LBW, or IUGR after adjusting for other major risk factors;

2. To examine whether such associations were confounded by exposures to copollutants;
3. To assess how much residual confounding affected the associations; and
4. To examine whether the associations were modified by temperature extremes, socioeconomic status (SES), or secondhand smoke (SHS) exposure.

STUDY DESIGN

Qian and colleagues chose a cohort and nested case–control design with which to test their specific aims. For the cohort study, the final population was 95,911 births that occurred during a 2-year period (June 2011 to June 2013). They were selected from an initial pool of 102,024 births to women whose residential addresses in the study area could be confirmed and excluded pregnancies with multiple births, stillborn infants, infants with extreme birth weights (<500 g or >5000 g), or extreme gestational ages (<20 weeks or >46 weeks).

The health outcomes of interest were PTB, defined as births occurring before 37 weeks of gestation; LBW, defined as infants weighing less than 2500 g; and IUGR, defined as infants whose birth weight fell below the 10th percentile of all singleton live births in Wuhan during the study period who were in the same stratum by sex and week of gestation as the control infants. The investigators reported the prevalence of PTB (not including LBW) in the cohort to be 4.5%, of LBW (not including PTB) to be about 3%, and of IUGR to be 8.8% (Critique Table 1). The prevalence rates for LBW and PTB in Wuhan were lower than in the United States, where they were 8.00% and 9.87%, respectively, in 2014 (*www.cdc.gov/nchs/fastats/birthweight.htm*); statistics on the prevalence of IUGR, which can be a function of factors affecting PTB, LBW, or both were not readily available for the United States.

The final study populations and numbers of adverse birth outcomes for the cohort and the case–control studies are summarized in Critique Table 1. The women in the cohort were selected from 98 communities within seven inner-city districts of Wuhan (see IR Appendix C for maps). For the case–control study, the investigators selected all PTB and LBW births; controls were randomly selected from the same inner-city districts and matched to cases by month of birth (one control for each case). The final set of cases and controls included in the study were those for whom the investigators were able to complete home visits and questionnaires (response rates were 57.7% for the cases and 69.3% for the controls). The case–control study did not include IUGR in its analyses.

Covariate Data

Detailed data were collected on all mothers in the cohort at the first prenatal visit and at delivery of the infants as part of the health care system in Wuhan. They were the source of the covariates referred to as "delivery data" in the report (see Critique Table 2). The covariate data collected have been identified as potential confounders or effect

Critique Table 1. Overview of Wuhan Study Populations for 2-Year Study Period (2011–2013)

Study Design	Total Births	Birth Outcomes (Number of Births)	Full Term or Normal Weight (Number of Births)
Cohort[a]	95,911	PTB: 4,308 LBW: 2,853 IUGR: 8,452	PTB: 91,603 LBW: 93,058 IUGR: 87,444
Case–control[b]	Total sampled: 11,606 Total interviewed: 7,409 (63.8%)[c]	Total cases sampled: 5,457 Total cases interviewed: 3,146 (57.7%)[c] PTB: Not specified LBW: Not specified	Total controls sampled: 6,149 Total controls interviewed: 4,263 (69.3%)[c]

[a] The cohort was selected from a pool of 102,024 births from which still births, birth defects, births with extreme birth weights (<500g or >5000 g), multiple births, or extreme gestation periods (<20 weeks or >46 weeks) were excluded.

[b] For the case–control study, only those births for which the investigators had completed home visits and questionnaires were included (5,567 total cases and 6,149 total controls). The percentages reflect the response rates in cases and controls.

[c] Percentages represent the number of individuals sampled who completed the interview and were therefore included in the case–control study.

Critique Table 2. Overview of Main Analyses Using Logistic Regression[a]

Aim	Description	Cohort or Case–Control	Dependent Variables (Dichotomous)	Exposure		Models/ Other Covariates	Multipollutant Models?
				Metric	Exposure Assignment		
1	Evaluate the effects of individual pollutants during vulnerable periods in pregnancy on adverse pregnancy outcomes	Cohort	PTB (<37 wks) LBW (<2500 g) IUGR[b]	**Continuous variable:** Daily mean $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3 Averaging times: full period of gestation, trimester, month[c]	**Nearest monitor:** Maternal residence at time of child's birth in community wholly or partially within 5 km (15 km for $PM_{2.5}$) of a monitoring station	**Model 1:** Crude **Model 2:** Main model, adjusted for covariate data collected at delivery[d]	Single-pollutant models
2	Same as Aim 1 but with two-pollutant models	Cohort	PTB LBW IUGR	Same as above	Same as above	Main model, adjusted for covariate data collected at delivery[d]	Two-pollutant models
3	Evaluate how residual confounding affected the associations	Nested case–control	PTB LBW No IUGR in the case–control study	**Dichotomous exposure variables**[e] Averaging times: full period of gestation, trimester (appendix only), month (appendix only)[c]	**Inverse distance weighted (IDW)** between maternal address at time of child's birth and 3 nearest monitors within 5 km	**Model 1:** Crude, no covariates **Model 2:** Adjusted for data at delivery[d] **Model 3:** Adjusted for delivery data and questionnaire data[f] **Model 4:** Two-phase models, corrected for nonresponses, adjusted for delivery data and questionnaire data	Single-pollutant models
4	Evaluate whether the associations are modified by extremes of temperature, SES, household income, or SHS exposure	Cohort	PTB LBW IUGR	**Continuous variable:** Daily mean $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3 Averaging times: full period of gestation, trimester, month[c]	**Nearest monitor:** Maternal residence at time of child's birth in community wholly or partially within 5 km (15 km for $PM_{2.5}$) of a monitoring station	Stratify by temperature at conception, maternal education, household income, SHS exposure Adjust for covariate data collected at delivery[d]	Single-pollutant models

[a] Most of the analyses reported were conducted using logistic regression. Analyses using linear regression are shown in Appendix M (Tables M.50 through M.52) available on the HEI Web site, but the authors argued against their use in the text.

[b] IUGR is defined as an infant whose birth weight falls below the 10th percentile of all singleton live births, between 2011 and 2013, in Wuhan who were in the same stratum by sex and week of gestation as the target infant.

[c] Averaging periods for exposure included (1) the full period of gestation from conception to birth; (2) trimester; and (3) the first, second, third, next-to-last, and last months of pregnancy.

[d] Delivery data included maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and ambient temperature during the week of conception.

[e] The cut points were values close to the pollutant medians and differed slightly by pollutant and outcome. For $PM_{2.5}$, they were 63.7 μg/m^3 (PTB) and 65.8 μg/m^3 (LBW); for PM_{10}, they were 99.5 μg/m^3 (PTB) and 96.6 μg/m^3 (LBW); for SO_2, they were 34.9 μg/m^3 (both PTB and LBW); for NO_2, they were 58.8 μg/m^3 (PTB) and 58.9 μg/m^3 (LBW); for CO, they were 987.5 μg/m^3 (PTB) and 1010.8 μg/m^3 (LBW); and for O_3, they were 70.8 μg/m^3 (PTB) and 72.3 μg/m^3 (LBW).

[f] Adjusted for covariates from the delivery data plus additional covariates from the survey including total household income, SHS exposure, maternal depression during pregnancy, and vaginal bleeding during pregnancy.

modifiers in other studies (Ritz et al. 2007). The final covariates included in the investigators' models were

- Maternal age,
- Maternal educational attainment,
- Maternal occupation,
- Parity,
- Gravidity,
- Infant sex,
- Season of conception, and
- Ambient temperature during the week of conception.

For the case–control study, the investigators collected additional data from mothers of cases and controls using a detailed questionnaire during home visits. These are referred to in the report and Critique Table 2 as "questionnaire data." The final questionnaire covariates selected were

- Total household income,
- SHS exposure during gestation, as a function of paternal smoking,
- Depression during pregnancy, and
- Vaginal bleeding during pregnancy.

The investigators selected these covariates for the case–control study analyses based on two criteria: (1) that "they are known or suspected to be risk factors for the adverse pregnancy outcomes" and (2) that "model analyses showed that these covariates, in combination, lead to changes in the estimated effects of more than 5% for some of the study pollutants." Data were also collected on, for example, active smoking and alcohol consumption in pregnancy, but these were almost never reported (<1%) and hence were not included in the analyses.

Exposure Assessment

The investigators obtained hourly air pollution and weather data from nine monitoring stations representing seven inner-city districts in the Wuhan Air Automatic Monitoring System from August 2010 to June 2013 (see IR Appendix C for maps of the area). Only two of these stations provided data on $PM_{2.5}$. All were located in what were considered to be urban background air pollution sites and thus away from local sources of air pollution. The investigators examined correlations between the individual pollutant concentrations measured at the monitoring stations.

The investigators matched dates in the air pollution records to the date of birth and to the first day of the last menstrual period in order to include potential dates of conception. Twenty-four-hour averages (8-hour averages for O_3) were calculated from the hourly data from each station. Critique Table 3 summarizes the average concentrations and interquartile range (25th to 75th percentile) for each of the pollutants across all monitoring stations over the entire period of the pregnancies in the cohort. The table also shows that the pollutant concentrations exceeded either current U.S. standards or international guidelines for all but CO and O_3.

Exposures to individual pollutants were assigned to mothers using different methods for the cohort and case–control studies. In the cohort study, daily mean concentrations were assigned from the monitor nearest to the residential community in which the mother lived at the time of the child's birth. The residential community needed to be wholly or partially within 5 km of the monitor for all pollutants except $PM_{2.5}$, for which the distance was 15 km. In the case–control study, daily mean concentrations were assigned based on an inverse distance weighted (IDW) average of the three closest monitors within 5 km of the mother's home address at the time of the child's birth. The criteria for estimating the $PM_{2.5}$ exposures from the two monitoring stations where $PM_{2.5}$ was measured were not described.

Exposures were estimated for three different time scales during the pregnancy to investigate possible sensitive time windows of exposure: for the entire gestational period from conception (starting 14 days after the first day of the last menstrual period) to birth, for each trimester (91-day periods), and for particular months (the first, second, and third months and the next-to-last and last months before birth).

Statistical Analyses

The investigators conducted a large number of analyses to investigate the various pollutants, exposure windows, covariates, and birth outcomes in the cohort and case–control studies; Critique Table 2 provides a comparative overview. For their main analyses in both the cohort and case–control data, they conducted logistic regressions, both crude and adjusted for various covariates, to estimate the associations between exposures to single pollutants and birth outcomes.

As indicated in Critique Table 2, the main analyses in the cohort were conducted for each of the three outcomes, PTB and LBW (combined and separately) and IUGR; the case–control study considered only PTB and LBW. In secondary analyses, the investigators also considered several other approaches to characterizing outcomes, using (1) term LBW, occurring only in women who had full-term pregnancies (because babies born pre-term are often also lower in weight); (2) birth weight (in grams) as a continuous variable; (3) gestational age (in days) as a continuous variable; and (4) a substudy of gestational age determined by ultrasound.

Critique Table 3. Comparison of Mean Air Pollutant Concentrations in Wuhan, China, with Ambient Air Quality Standards and Guidelines

	Air Pollutant Concentration in Wuhan				
Pollutant	Annual Average 24-hr Concentration[a] (μg/m^3)	25th Percentile	75th Percentile	U.S. EPA NAAQS	WHO AQ Guidelines
$PM_{2.5}$	70.8	62.2	75.7	15 μg/m^3, annual mean 35 μg/m^3, 24-hr mean	10 μg/m^3, annual mean 25 μg/m^3, 24-hr mean
PM_{10}	101.9	93.4	108.4	150 μg/m^3, 24-hr mean	20 μg/m^3, annual mean 50 μg/m^3, 24-hr mean
SO_2	35.3	30.8	38.8	0.5 ppm (1,410 μg/m^3), 3-hr mean	20 μg/m^3, 24-hr mean 500 μg/m^3, 10-min mean
NO_2	58.8	53.9	63.7	100 ppb (188 μg/m^3), 1-hr mean 53 ppb (99.64 μg/m^3), annual mean	40 μg/m^3, annual mean 200 μg/m^3, 1-hr mean
CO	1012.4	926.6	1097.8	9 ppm (11,100 μg/m^3), 8-hr mean 35 ppm (43,200 μg/m^3), 1-hr mean	No guideline
O_3	75.0[b]	63.5	85.3	0.070 ppm (148 μg/m^3), 8-hr mean	100 μg/m^3, 8-hr mean

[a] Source: IR Table 3.

[b] 8-hr average.

Abbreviations: AQ = air quality; U.S. EPA NAAQS = United States Environmental Protection Agency National Ambient Air Quality Standards; WHO = World Health Organization.

The cohort models were adjusted only for the delivery variables, identified earlier in the Covariate Data section.

For the case–control study, the investigators considered four models: a crude model (model 1); a model adjusted for delivery covariates only, as in the cohort data (model 2); a model adjusted for both the delivery and questionnaire covariates (model 3); and a two-phase model adjusted for both the delivery and questionnaire covariates (model 4). The first three used only the cases and controls, selected as described in the Study Design section, and were analyzed using logistic regression. The fourth modeling approach was patterned on two-phase analyses of birth outcome data reported by Hoggatt and colleagues (2009) and Ritz and colleagues (2007), to reduce the potential for biases that might have been introduced by different rates of nonresponse to the questionnaires among the cases and controls (i.e., nonresponse bias). This analysis used a set of variables (outcomes, covariates, and exposures) from the cohort (first phase) to guide the stratified random sampling of cases and controls (second phase) and, ultimately, a two-phase analysis in which the proportions of cases and controls in each stratum served as weights in the statistical analysis, in essence to adjust for any differences between the characteristics of final cases and controls who responded to the

survey and those of the original cohort (model 4). Comparisons of the results of model 4 with those of the original case–control sample without weighting analyses (models 2 and 3) and with those of the full cohort gave insight into the potential magnitude of the nonresponse bias. The investigators describe the two-phase sampling approach for the cases and controls in IR Appendix L; however, details of the specific stratification variables, inverse probability weighting, and form of the two-phase statistical model were not provided.

In addition to the differences in methods for exposure assignment noted earlier in the Exposure Assessment section, the investigators' primary analyses characterized exposures differently in the cohort and the case–control models. In the cohort study, maternal exposures were modeled as continuous variables. In the case–control study, maternal exposures based on IDW were modeled as dichotomous variables with cut points chosen close to the median concentration of each pollutant in Wuhan (see Critique Table 2 footnote for these cut points).

At the request of the Committee, the investigators conducted two additional analyses using different exposure metrics. First, they analyzed the case–control study data using continuous exposure variables to provide a more direct comparison with the models used in the cohort study, as in a standard nested case–control study; those results are presented in IR Appendix Table O.36, available on the HEI Web site. Second, they analyzed the cohort study with tertiles of exposure to gain insight into the shapes of the concentration–response relationships; those results are presented in IR Appendix Tables M.54–M.59.

In order to address specific aim 2, regarding the role of copollutants, the investigators extended their logistic regression analyses in the cohort data to two-pollutant models, systematically examining the various pairwise combinations of pollutants. Two-pollutant models were not examined in the case–control study.

The case–control study design was intended to help provide answers to specific aim 3, by enabling the authors to examine additional individual-level covariates that were available from the detailed questionnaires administered to mothers of babies identified as cases and controls (i.e., the questionnaire data, described earlier). The investigators noted that they did not adjust for other variables that are often included in other birth outcome studies (e.g., marital status, race, prenatal care, maternal smoking, or alcohol use), because either the population was quite uniform with respect to these variables or the risk factors (maternal smoking and alcohol use) were extremely rare in the questionnaire responses.

To address specific aim 4, the investigators conducted analyses with the cohort data to evaluate whether the associations of individual pollutants with adverse birth outcomes were modified by temperature extremes at the time of conception, SES, or SHS exposure. Specifically, they examined the direct effect of average daily temperature during the week of conception on PTB, LBW, and IUGR and its interaction with exposures to each of the air pollutants measured over the entire pregnancy. Temperature data during the week of conception were classified as low (<3.8°C; <5th percentile), normal (≥ 3.8°C to ≤ 31.6°C), or high (>95th percentile; >31.6°C).

They reported the results of their regression analyses as odds ratios (ORs) with 95% confidence intervals, tested against a two-tailed significance level of 0.05.

OVERVIEW OF MAIN RESULTS

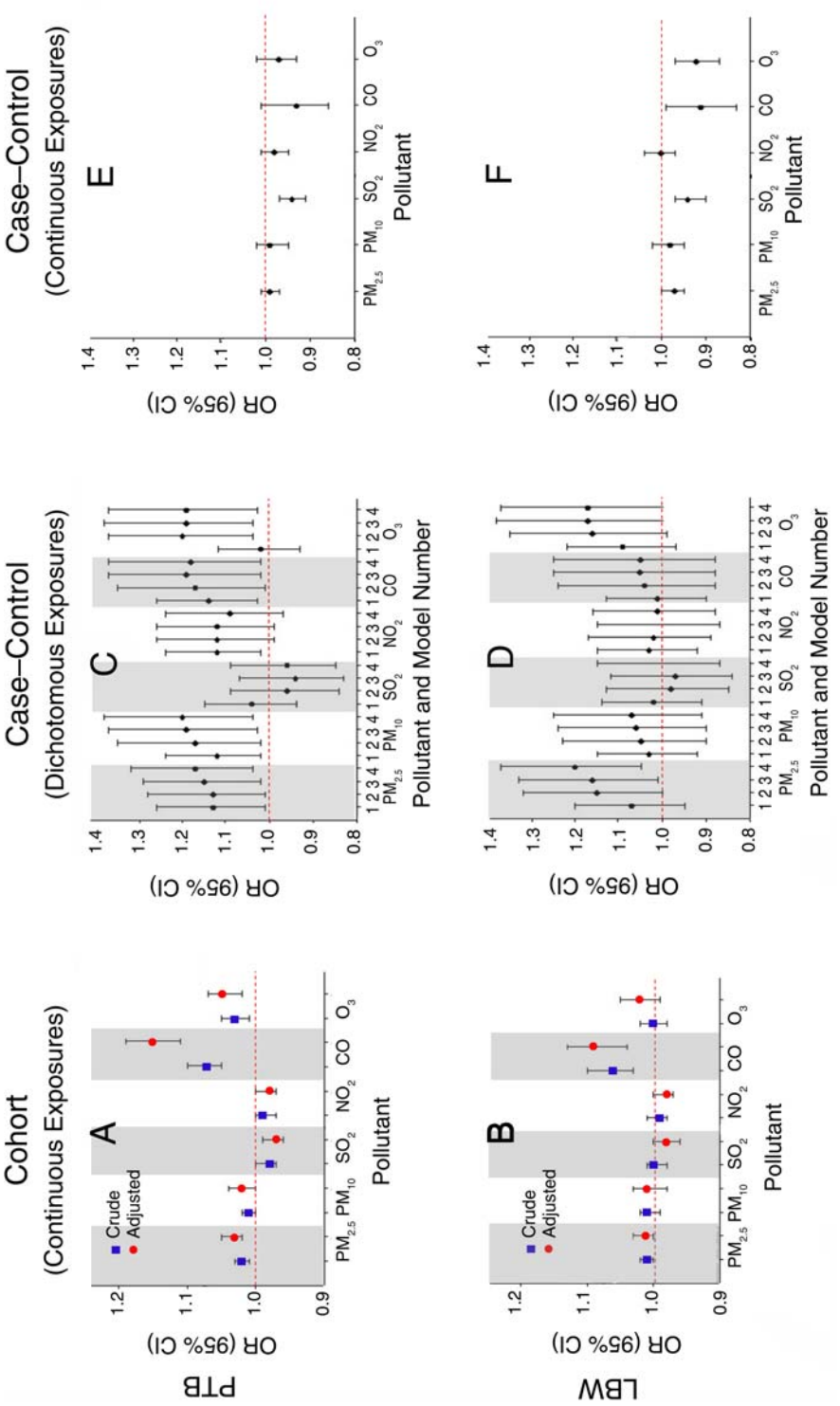
Aim 1. Association of Individual Pollutant Exposures with Adverse Birth Outcomes

The investigators summarized their main cohort study results in IR Table 1. The table reports associations of the individual pollutants with PTB, LBW, and IUGR over the course of the entire pregnancy and for selected time windows of exposure, using either crude models or models adjusted for potential confounding covariates. The PTB and LBW results for exposure over the entire pregnancy are also plotted with their 95% CIs in the left-hand column of the Critique Figure, panels A and B, respectively. IUGR results are not shown.

Entire Pregnancy The investigators concluded that the results of the cohort study showed small increases in the adjusted ORs for PTB associated with increases in exposure to $PM_{2.5}$ (per 5 μg/m^3), PM_{10} (per 5 μg/m^3), CO (per 100 μg/m^3), and O_3 (per 10 μg/m^3) over the entire pregnancy from conception to birth (see the Critique Figure, panel A). The odds of preterm birth were null or decreased for SO_2 and NO_2. These results for PTB have been published separately elsewhere (Qian et al. 2016).

The investigators also reported small average increases in the adjusted odds of LBW for exposures over the entire pregnancy to $PM_{2.5}$ and to CO but not to PM_{10}, O_3, SO_2, or NO_2 (see the Critique Figure, panel B). The investigators reported small decreases in the odds of IUGR for $PM_{2.5}$, PM_{10}, NO_2, CO, and O_3 but an increase in the odds of IUGR for SO_2 (IR Table 1).

Vulnerable Exposure Windows In IR Table 1, the investigators reported only selected monthly or trimester results for each pollutant, presumably based on statistical significance.



Critique Figure. Comparison of results for PTB and LBW from cohort and case–control studies. Cohort continuous exposures (panels A and B): ORs were estimated based on per 5-µg increase in $PM_{2.5}$ and PM_{10}, 3-µg increase in NO_2 and SO_2, 10-µg increase in CO. Exposures were modeled as continuous variables based on nearest monitor (source: IR Table 1). **Case–control dichotomous exposures (panels C and D):** Exposures were modeled as dichotomous variables based on IDW exposures. In model 1, ORs were estimated as the increase in the crude odds. Model 2 adjusted for covariates from the delivery data, including maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and ambient temperature during the week of conception. Model 3 adjusted for covariates from the delivery data plus additional covariates from the survey, including total household income, SHS exposure, maternal depression during pregnancy, and vaginal bleeding during pregnancy. Model 4, a two-phase model, adjusted for covariates from both the delivery data and survey data in model 3 (source: IR Table 7). **Case–control continuous exposures (panels E and F):** Exposures were modeled as continuous variables based on nearest monitor and were adjusted for covariates from the delivery data, including maternal age, maternal educational attainment, maternal occupation, gravidity, parity, infant sex, season of conception, and ambient temperature during the week of conception. Crude models were not presented (source: IR Appendix Table O.36).

Judging from the results presented, there was some suggestion of effects of exposure in the second trimester to $PM_{2.5}$, PM_{10}, and CO on PTB and LBW and of exposure in the first trimester to PM_{10}, SO_2, NO_2, and CO on IUGR. Given the absence of consistent patterns, the investigators considered these analyses to be generally inconclusive.

Analysis by Tertiles of Exposure The investigators reported that the results of their tertile analyses supported the basic findings of the cohort study, citing increased odds of PTB and LBW at the highest tertiles for $PM_{2.5}$ and CO in particular. For $PM_{2.5}$, they did find evidence of monotonically increasing concentration–response function — that is, ORs increased with increasing concentration tertiles. Their findings for the remaining pollutants, however, suggested nonlinearities in the concentration–response functions for both endpoints. They observed significant protective effect estimates (ORs less than 1) in the middle tertiles of exposure but either no effect or increased risks of PTB or LBW at the highest tertiles of exposures for the other pollutants (IR Appendix Tables M.54–M.59). The protective or null results for NO_2 and SO_2 were broadly comparable to those in the cohort and case–control studies, in particular for LBW.

Aim 2. Two-Pollutant Models

The investigators' analyses of the cohort data using two-pollutant models showed little or no effects of adjusting for a second pollutant on the adjusted ORs for LBW, PTB, or IUGR associated with exposures over the entire pregnancy (IR Table 5). Pairwise correlations between annual average concentrations of most pollutants were moderate to high (correlation coefficients 0.50–0.82) over the study, except for those with O_3, which indicated weak negative correlations (IR Table 2). High correlations make it difficult to gain insights into the independent effects of individual pollutants in two-pollutant models.

Aim 3. Analysis of the Case–Control Study and Residual Confounding

The investigators used the case–control data to explore the main effects of individual pollutant exposures on PTB and LBW and to assess the potential for residual confounding using the four models described in the Statistical Analyses section above. Their primary analyses estimated the odds of PTB and LBW associated with exposures calculated for the entire pregnancy, expressed as dichotomous variables. The results are shown graphically in the Critique Figure, in panel C for PTB and in panel D for LBW (numerical details can be found in IR Table 7).

The investigators reported increased odds of PTB associated with exposures above the median concentrations of $PM_{2.5}$, PM_{10}, NO_2, CO, and O_3 for most models (Critique Figure, panel C). Adjusted models for SO_2 suggested lower odds of PTB on average, but the odds were also consistent with no association. The adjusted odds of LBW were elevated for $PM_{2.5}$ and O_3 (models 2, 3, and 4) and were consistent with no effects for PM_{10}, SO_2, NO_2, and CO (Critique Figure, panel B). The investigators suggested that the larger effect estimates in the case–control study compared with those observed in the cohort study may in part be attributable to the use of dichotomous exposures rather than the continuous exposure variables used in the cohort study. However, this explanation is difficult to evaluate without more information on the differences between the mean concentrations for subjects below and above the chosen cut points. Differences between the mean crude and adjusted findings were greatest in the models adjusting for the delivery covariates. The investigators concluded from the results of the case–control analyses that there was little residual confounding by the additional covariates they collected from the questionnaires. The adjustment for additional covariates from the questionnaire (model 3) led to minor changes in the ORs from analyses with the delivery covariates alone (model 2) (see the Critique Figure, panels C and D). From comparisons of the two-phase model results (model 4) with those of the logistic regression with both sets of covariates (model 3), they concluded that the differences in ORs were small, indicating little bias from differential responses in the cases and controls compared with those from the full set of births in the Wuhan cohort.

A nested case–control design ordinarily addresses this specific aim through a direct comparison of the cohort and the case–control results, based on use of the same exposures and analytic approach. In this study, it is theoretically addressed by comparison of the cohort results with those of the two-phase analysis (model 4).

As discussed earlier, at the request of the Committee, the investigators also performed a more conventional analysis of the case–control data using the continuous concentration variables, assigned to subjects based on the nearest monitor, as in the cohort analyses. The results are shown in panels E and F of the Critique Figure (numerical details can be found in IR Appendix Table O.36). They reveal sharp differences from what had been observed in the cohort study or in the case–control study analyzed with the dichotomous exposure variables above, particularly for $PM_{2.5}$, PM_{10}, CO, and O_3 where the results now suggest no effect or weakly protective effects of exposures on PTB or LBW.

Aim 4. Evaluation of Effect Modification by Temperature Extremes, SES, and SHS

The investigators reported in IR Table 8 that there was no consistent pattern of effect modification by temperature at conception of the individual air pollutant effects on PTB and LBW in their analysis conducted with the cohort data. The *P* values for the interactions were difficult to reconcile with the OR results; for example, the *P* value for the interaction of temperature with $PM_{2.5}$ on LBW was highly significant ($P < 0.01$) when all the ORs indicated no effect.

The investigators reported no consistent patterns in the effect of SES, measured as maternal educational attainment or by household income, on the ORs for PTB, LBW, or IUGR across the various pollutants (IR Table 9 and Table 10, respectively). The investigators also found no clear pattern of interactions between pollutant exposure and maternal exposure to SHS on the risks of PTB or LBW (IR Table 11).

HEALTH REVIEW COMMITTEE EVALUATION

In its independent review of the study, the Committee commended Qian and colleagues for having created a large cohort with which to examine their hypotheses about the effects of air pollution and other key covariates on the three adverse birth outcomes: PTB, LBW, and IUGR. The potential impact of air pollution on these important indicators of fetal health is of growing interest, and their cohort offered the opportunity to explore vulnerabilities associated with various time windows of exposure and to assess the modifying effects of temperature extremes at conception, SES, and maternal exposure to SHS.

The investigators started with a strong study design and sought to structure their analyses in ways that would allow comparisons with other studies of adverse reproductive outcomes (e.g., use of the same exclusion criteria for selecting individuals into the cohort, similar statistical analyses, and exposure intervals over which the effects were reported). In both their Introduction and Discussion sections, they undertook extensive efforts to review the relevant literature and to put their results in a broader context. They were responsive to the Committee's requests for revisions and for additional sensitivity analyses. HEI's quality assurance/quality control audit of the study indicated that the data for the study were collected with a high regard for data quality.

In its evaluation of the report, however, the Committee had fundamental concerns about the basic design and analyses that undermined its confidence in the results despite the investigators' efforts to address those concerns in subsequent revisions. This Critique therefore focuses on the primary design and analyses conducted to address the specific aims of the study and their implications for interpretation of the results.

STUDY DESIGN

A nested case–control design is strong because it offers the opportunity to collect more detailed, individual-level data on risk factors that are often prohibitively expensive to collect on all individuals in a large cohort but that could be important confounders or risk modifiers of the main outcomes of interest. The current study collected the additional data by having the mothers complete questionnaires after the births of their children. A strength of the study was that the investigators were able to question the mothers directly and did not need to rely on next of kin or other proxies, as do studies of fatal outcomes such as lung cancer.

Comparison of the results of the cohort analyses with those of its nested case-study control study (unadjusted and adjusted for the additional individual-level covariates) can provide insight into whether residual confounding by these covariates exists in the larger cohort study. However, a valid comparison for this purpose requires that other variables in the cohort and case–control samples remain the same. In this study, the investigators made a number of analytical decisions that caused their main cohort and case–control analyses to differ in important ways other than the inclusion of the additional covariates.

With the exception of one analysis requested by the Committee and provided in an appendix (IR Appendix Table O.36), the cohort and case–control analyses provided in the report cannot be interpreted as they would be in a standard nested case–control study. As the Committee has noted earlier in this Critique, the one direct comparison revealed results that were very different between the cohort and the nested case–control study. Had this and other analyses not raised numerous questions about the comparability of the data and analysis approaches, it might have been reasonable to evaluate the report as a suite of alternative approaches to analyzing the Wuhan data. However, under the circumstances, it was difficult to do so.

EXPOSURE ASSESSMENT

The assignment of exposures to subjects on the basis of nearest monitors or the use of IDW are both methods that have been employed in other studies, particularly for PM and O_3. Some degree of misclassification or error in the estimation of subjects' exposures is inevitable with either

method, but it is difficult to know from the information presented in the report whether one method was likely to provide a more accurate measure of exposure than the other. The availability of only two monitors for $PM_{2.5}$ raises some concern about how well differences in $PM_{2.5}$ exposures are represented in the study population. In addition, neither approach captures the fine-scale, within-city exposure contrasts that may be important for pollutants like NO_2 that are more variable spatially. For such pollutants, the methods used in this study may introduce substantial exposure misclassification and may explain why the study's results differed from those in other studies of birth outcomes that have attempted to develop more spatially resolved exposure estimates at the address level using denser monitoring networks and land-use regression models (see, for example, Pedersen et al. 2013 and Savitz et al. 2014).

Similarly, both inclusion of exposures in the statistical models as continuous variables (as in the cohort study) and as dichotomous variables (as in the case–control study) are acceptable approaches that have been used in other studies. However, the investigators' decision to use both further contributed to the lack of comparability between the cohort and the case–control study results. The rationale given for this decision was that the two-phase analysis conducted required dichotomous variables, and so they were used for all four models to make the results comparable. The Committee was not convinced that there is a requirement for covariates to be dichotomous in two-phase study analyses (see, for example, Haneuse et al. 2011).

The differences in how exposures were modeled and assigned to mothers and in how exposure variables were specified in the statistical models in the cohort and case–control studies meant that the study did not serve the purpose of a nested case–control design, in which treatment of exposure is the same and the main purpose is to evaluate the effect of controlling for residual confounding.

ADVERSE BIRTH OUTCOMES

The choice of adverse birth outcomes to study was generally appropriate, although the overlap between PTB and LBW can lead to complications in interpretation (i.e., PTB may often lead to LBW, creating challenges for understanding whether air pollution is affecting gestational age or birth weight directly via some other mechanism). More recent studies have favored the use of the outcome "term LBW" (i.e., LBW in infants who have been carried for the full term). The authors' addition of the Venn diagrams (IR Appendix Figures M.1 and M.2) helped clarify the degree of overlap between PTB and LBW in particular. The addition of the sensitivity analysis using term LBW as an outcome (IR Appendix Table M.49) provided both some reassurance that their choice of LBW did not create substantial bias and a point of comparison with other studies that more typically use term LBW. IUGR is a less specific and difficult diagnosis, which may contribute to the lack of significant associations with pollutants in this category.

STATISTICAL ANALYSES

The Committee thought the investigators' use of multivariate logistic regression models for the main analyses in the cohort study was generally appropriate, given the binary nature of the outcomes (e.g., less than or greater than 2500 g) being studied. However, the apparent nonlinearities in the exposure–response functions for most pollutants suggested by the tertile analyses in IR Appendix Tables M.54–M.59 created some challenges for the interpretation of the case–control results. The exposure–response function in the linear predictor of the logistic model is assumed to be linear, while the tertile analysis suggests the underlying relationship was not linear. A potential complication with the tertile analyses is that the reference exposures were already quite high for some pollutants. A related point is that, when nonlinearities exist and exposures are collapsed into dichotomous variables, as they were in the case–control study, results can be sensitive to the choice of the cut points. When exposure is modeled as a continuous variable in logistic regression models, as it was in the cohort study, these do not necessarily cause problems. In general, however, the report provided very little information that would enable evaluation of the modeling choices, in particular, information on goodness of fit for the various models.

The Committee thought the investigators' effort to identify potentially confounding covariates for both the cohort and case–control studies based on theory and on findings from other studies was a reasonable first step. However, the Committee found it difficult to determine how the final selections of covariates were made for the cohort and case–control studies, in particular when the selections were made on the basis of the effects of various covariates "in combination." No details were provided about the methods used for, or the results of, this selection process. The Committee did agree with the investigators' decisions not to include maternal smoking or alcohol consumption, both associated with adverse birth outcomes in other studies, given the very low rates of both among women in the Wuhan population. The selection of exposure to SHS from paternal smoking was a better choice.

Adjustment for covariates alone may not take into account the impact of potential bias introduced by nonresponse rates in the cases and controls. The concern is that

the cases and controls might differ in important ways not only from each other, but also from the original cohort in ways that bias the results in one direction or another. The investigators' implementation of a two-phase analysis (Hoggatt et al. 2009; Ritz et al. 2007) was a step toward addressing this concern. However, the report did not give a clear indication of how the two-phase analysis tackled the nonresponse. That is, key information on the stratification variables used to select the cases and controls, to establish weights for the statistical analyses, or other details of the actual two-phase statistical analyses performed were not provided. Furthermore, Hoggatt and colleagues (2009) and Ritz and colleagues (2007) drew some of their conclusions about the effect of nonresponse bias by comparing the results of two-phase analyses with the results of cohort analyses, which was not possible in this report, given the differences in exposure metrics used. Consequently, the Committee was unable to evaluate whether or not the analysis met its goal of addressing potential bias from nonresponses. If nonresponse bias was not a problem, then the Committee would agree with the investigators that the simpler logistic regression models appear to be sufficient for the case–control analyses.

RESULTS AND INTERPRETATION

The investigators in effect conducted their evaluation of the Wuhan data using separate cohort and case–control studies, not an integrated nested case–control study. Even though the interpretations of the ORs from the two studies were different, one can still ask whether their two sets of findings are qualitatively similar to one another or are otherwise consistent with findings from other studies with similar designs.

Taken at face value, there are some similarities between their cohort and case–control study results for both PTB and LBW. Both sets of results suggested that increases in exposure to $PM_{2.5}$, PM_{10}, CO, and O_3 over the full pregnancy were associated with small increases in the odds of PTB and LBW. But the cohort study also suggested associations between exposures to PM_{10} and O_3 and increased odds of PTB, whereas the case–control study did not. The Committee noted that the confidence intervals were substantially wider in the case–control study, given the smaller numbers of subjects. Both studies suggested significantly increased odds of LBW associated with increased exposures to $PM_{2.5}$, but not to PM_{10}, which was surprising, given how correlated these pollutants are. They also differed in their findings for CO and O_3.

In the cohort study, the adjusted ORs for exposures to SO_2 and NO_2 suggested that these pollutants either had no effect or might even improve outcomes for PTB and LBW, which, in the case of NO_2, is at odds with findings from more recent studies with which the investigators compared their work (e.g., Pedersen et al. 2013 and Savitz et al. 2014). One explanation may be that Qian and colleagues had to rely on central site monitors, whereas Pedersen and colleagues (2013) and Savitz and colleagues (2014) deployed a dense network of NO_2 monitors as well as advanced exposure modeling for a pollutant that is known to be highly variable spatially. In contrast with the cohort study, the case–control study did suggest increased odds of PTB associated with exposures to NO_2, meaning that greater exposure misclassification would not seem to be an explanation here. Except for exposure to SO_2, the results for IUGR suggested that exposure to air pollution generally reduced the odds of observing that particular outcome.

Ultimately, however, the study was originally conceived as a nested case–control study, not as two distinct studies. And when analyzed as a nested case–control study — that is, when the case–control data were analyzed using the same continuous exposure variables, covariates, and statistical methods as in the cohort — the results were dramatically different from the other two sets of results (Critique Figure, panels E [PTB] and F [LBW], and IR Appendix Table O.36 [on the HEI Web site]). These differences occurred even without inclusion of the additional questionnaire covariates available for the cases and controls.

The investigators suggested that the comparison in IR Appendix Table O.36 was invalidated by potential biases resulting from the differential response rates in the cases and controls, something that was not accounted for in this analysis. The Committee was not convinced; at least, this explanation is inconsistent with the investigators' conclusions from their two-phase analysis (IR Table 7, comparisons of models 3 and 4) that the differences in response rates were not contributing to substantial bias. The Committee noted that this conclusion was based on analysis of exposure as a dichotomous variable and that the results might have been different if the exposure were modeled as a continuous variable. These questions might be clarified by further exploration and analysis of these results by the investigators.

Other analyses also raised questions. The analyses by tertiles of exposure (IR Appendix Tables M.54–M.59), for example, which were designed to provide insight into the exposure–response relation at different levels of exposure, essentially found increased risks only at the highest levels of exposure for some pollutants and reductions in risk in the middle tertile for most pollutants, despite the fact that the midlevel exposures were higher than those in birth outcome studies in other parts of the world.

In general, the investigators' choices about which data and results to present in the report created a challenge for the Committee in trying to piece together potentially important conclusions. In some cases, key details, such as the cut points used to create the dichotomous exposure variables for the case–control analyses, are found only in the footnotes of IR Table 7 and were not well explained in the text. In other cases, as discussed earlier, critical details are found only in the extensive appendices, in particular the only analyses of the cohort and the case–control study using comparable exposures and statistical models (IR Appendix Table O.36).

CONCLUSIONS AND RECOMMENDATIONS

This study set out to answer important questions about the role that air pollution exposure might have on three measures of adverse birth outcomes — LBW, PTB, and IUGR — in a large cohort of mothers and newborns in Wuhan, China. The investigators also sought to evaluate the potential for confounding of the main associations of individual pollutants with adverse birth outcomes by copollutants and by various individual-level risk factors. They further explored whether SES factors, maternal exposure to SHS, or extremes of temperatures might modify any of those associations. With a large cohort in a region of China with high levels of several air pollutants, high temperatures, and detailed covariate data, the investigators were well poised to address these questions. The investigators sought to pattern their work on other studies of birth outcomes, were very responsive to questions from the Committee, and provided many additional analyses and explanations.

In the Committee's view, however, given the concerns raised in the previous sections, the study was unable to answer with confidence several of the specific aims it set out to address. Specifically, although the separate cohort and case–control studies provided weak evidence of adverse effects of air pollution during the full pregnancy on PTB and LBW that were similar to those that have been observed in other studies, when analyzed as a nested case–control study using the same exposure metrics, no effects were observed. These findings then raise concerns about the ability to draw conclusions from the analyses conducted to address other specific aims, such as the effect of residual confounding and the ability to assess effect modification by temperature extremes, SES, and SHS. Consequently, any individual findings from the cohort and case–control studies should be considered suggestive rather than conclusive, and should be interpreted carefully together.

ACKNOWLEDGMENTS

The Health Review Committee thanks the ad hoc reviewers for their help in evaluating the scientific merit of the Investigators' Report. The Committee is also grateful to Sumi Mehta and Aaron Cohen for their oversight of the study, to Katy Walker for her assistance in preparing its Critique, to Kathryn Liziewski for research assistance on the Critique, to George Simonson for his science editing of the Report and its Critique, and to Hope Green, Fred Howe, Hilary Selby Polk, and Ruth Shaw for their roles in preparing this Research Report for publication.

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Number 189
September 2016