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Review article

Association between ambient air pollution and pregnancy complications: A systematic review and meta-analysis of cohort studies

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ABSTRACT

Background: Pregnancy complications, such as gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP), have a great impact on public health. Exposure to ambient air pollution during pregnancy may cause pregnancy complications. The aim of our study is to explore the risk of trimester-specific maternal exposure to air pollutants on complications of pregnancy.

Methods: PubMed, EMBASE, Web of Science, and Cochrane were systematically searched for cohort studies published before October 27, 2019 which reported the association between ambient air pollutants ($PM_{2.5}$, PM_{10}, CO, NO, NO_2, NO_x, O_3, and SO_2) and pregnancy complications (GDM, HDP, preeclampsia, and gestational hypertension) during different exposure windows. A meta-analysis was applied to combine relative risks (RRs) and their confidence intervals (CIs) from eligible studies. Quality assessment was conducted and Egger test was used to evaluate the publication bias. All statistical analyses were performed by STATA software (Version 15, StataCorp, College Station, Texas, USA).

Results: This meta-analysis consisted of 33 cohort studies conducted on 22,253,277 pregnant women. Meta-analyses showed during the first trimester, there were significant associations of PM_{10} with gestational hypertension (RR = 1.07, 95% CI: 1.02–1.12 per 10 μg/m^3, I^2 = 0.0%), of SO_2 with GDM (RR = 1.04, 95% CI: 1.00–1.08 per 1 ppb increment, I^2 = 54.1%), of $PM_{2.5}$ with preeclampsia (RR = 0.97, 95% CI: 0.95–1.00 per 5 μg/m^3, I^2 = 4.1%). During the entire pregnancy, $PM_{2.5}$ significantly increased the risk of hypertensive disorders of pregnancy (RR = 1.18, 95% CI: 1.02–1.34 per 5 μg/m^3, I^2 = 85.1%). Egger test indicated that wide-scale publication bias was unlikely.

Conclusion: Maternal exposure to ambient air pollutants is associated with pregnancy complications especially during the first trimester. Further large multicenter cohort studies considering different constituents of pollutants, levels of disease severity, sensitive populations, and various exposure windows are warranted in the future research.

1. Introduction

Cardiovascular disease (CVD) related morbidity and mortality rates have decelerated or even declined in some countries over the past few decades (Benjamin et al., 2018; McClellan et al., 2019; Timmis et al., 2018). Nonetheless, the trend of CVD is not consistent among different subgroups. In children and young women, the increased prevalence of CVD has been acknowledged (George et al., 2017; Hollier et al., 2019). The prevalence of GDM ranges globally from 5.8% to 12.9% (Amro et al., 2016; Roberts et al., 2013). In the United States, HDP complicates up to 10% of pregnancies (Zhu and Zhang, 2016). Preeclampsia (PE), a pregnancy multisystem disorder, is characterized by hypertension

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unique and proteinuria during the second half of pregnancy, affecting 3–5% of all pregnancies (Ananth et al., 2013). The prevalence of hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM) is rising worldwide, and it is associated with health risks and responsible for a significant burden, such as the future development of CVD and cardiometabolic disorders later in life among both maternal and child health (George et al., 2017; Hollier et al., 2019).

Pregnancy complications have been reported to be associated with adverse pregnancy and birth outcomes, such as preterm birth, low birth weight, small for gestational age and fetal growth restriction (Lisonkova and Joseph, 2013; Odegard et al., 2000; Sibai, 2006). Several researchers have also found some other associated factors, such as maternal age, dietary intake, and body mass index, but these factors do not explain the cyclical pattern of seasonal changes in the risk of these pregnancy complications. Seasonal and meteorological fluctuations in air pollution have been reported (Coulibaly et al., 2015).

Air pollution has become a major environmental health problem affecting everyone, especially vulnerable pregnant women. The World Health Organization estimates that the reduction in life expectancy due to exposure to $PM_{2.5}$ is 8.6 months for countries in Europe (WHO, 2013). Several epidemiologic studies have found the relationship of trimester-specific ambient air pollution [particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), particulate matter less than 10 μm (PM_{10}), carbon monoxide (CO), nitrogen oxides (NO_X), nitrogen monoxide (NO), nitrogen dioxide (NO_2), ozone (O_3) and sulfur dioxide (SO_2)] and pregnancy complications (including HDP, GDM, PE, and GH). However, the studies of associations between air pollution and pregnancy complications have less conclusive or even inconsistent results (Abdo et al., 2019; Jo et al., 2019; Mendola et al., 2016; Nobles et al., 2019; Savitz et al., 2015; Wu et al., 2011). A meta-analysis (last search: October 2017) (Mohamed, 2019) involving 8 articles showed exposure to NO and SO_2 was associated with GDM. Another meta-analysis (last search: December 2013) (Pedersen et al., 2014) involving 10 articles showed NO_2 increased the risk of HDP and preeclampsia during the entire pregnancy, CO and O_3 increased the risk of HDP during the first trimester. However, several new studies have been published on the associations between air pollutants and HDP or GDM since the last two reviews. Moreover, the number of studies on GH has been sufficient to analyze it as a separate outcome.

Given the critical exposure windows on health effects, it is plausible that ambient air pollution may increase the risk of these pregnant complications during different trimesters and the whole pregnancy. To provide high-quality and reliable evidence, we performed the current meta-analysis on cohort studies to investigate the effects of trimester-specific exposure to ambient air pollution on HDP, GDM, preeclampsia, and GH independently and provide coherent and consistent evidence for tackling the health effects of ambient air pollution.

2. Methods

2.1. Search strategy

We conducted this study by using the standard methods following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (Shamseer et al., 2015). We searched articles published before October 27, 2019 in the following electronic bibliographic databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. The Medical Subject Heading (MeSH) terms “Hypertension, Pregnancy-Induced”, “Pre-Eclampsia”, “Eclampsia”, “Diabetes, Gestational”, “Air Pollution”, and “particulate matter”, and non-MeSH terms concerning air pollution (i.e., $PM_{2.5}$, PM_{10}, CO, NO, NO_2, NO_x, O_3, and SO_2) and pregnancy complications (i.e., Gestational Hypertension, Gestational Diabetes Mellitus, GMD, GH, and HDP) were used. All searching terms related to pregnancy complications were connected using “OR”, and so were the terms related to air pollution. Then we applied “AND” to combine the results of the above two parts. We adjusted and confirmed retrieval strategies according to different databases after preretrieval tests of the search terms. Additionally, we manually searched previously published systematic reviews to find potentially eligible studies.

2.2. Selection criteria

Two authors (BW and LYY) conducted study selection, and differences between them were resolved by the third author (NYL). At first, all retrieved articles were screened for the eligibility by reviewing the titles and abstracts after deleting duplicates. Then the full paper of the potentially eligible remaining references was further evaluated according to the following criteria.

Inclusion criteria: (1) the study design must be cohort studies; (2) studies explored the associations between air pollution (at least one of these pollutants: $PM_{2.5}$, PM_{10}, CO, NO, NO_2, NO_x, O_3, and $SO_{2)}$ and complications of pregnancy (at least one of these diseases: GDM, HDP, GH, and preeclampsia); (3) studies must focus on outdoor air pollution but not indoor; (4)diseases had to be diagnosed by physicians or there were clear medical records; (5) studies conducted analyses in the period of entire pregnancy and/or different exposure windows (the first, second, or third trimester); (6) studies provided relative risks (RRs) or odds ratios (ORs) and their 95% confidence intervals (CIs) with per standard deviation (SD), interquartile range (IQR) or other specific unit change of the pollutants level. Exclusion criteria: (1) case reports, conference abstracts, letters, and reviews; (2) repeat articles; (3) animal studies; (4) studies only examined exposure by traffic density data (e.g. within 250m of a major road vs beyond 250m) or ecologic assessment (e.g. high vs low) because we cannot conduct effect synthesis from these kinds of studies.

2.3. Data extraction and quality assessment

Data were extracted by two independent authors (BW and LYY) and conflicts were adjusted by a third author (DY). Each author used a standardized data extraction table to extract relevant information from eligible studies. The following information was extracted: the first author, publication year, country, duration of data collection, outcome, the type of pollutants, sample size, number of cases, exposure window, effect estimates (ORs/RRs and their 95% CIs), and adjusted covariates.

Two independent authors carried out the quality assessment following the Newcastle-Ottawa Scale (NOS) for cohort studies, and discordances were discussed by a third reviewer (YX) and resolved by consensus. The score of NOS ranges from zero to nine. The score greater than seven was categorized as “high quality”; otherwise, the study was classified as “low quality” (Flores-Pajot et al., 2016).

2.4. Statistical analysis

The idea that HDP includes gestational hypertension (GH) and preeclampsia (PE) has been widely accepted. Nevertheless, it is still controversial whether GH and PE are separate conditions or different spectrum of a single disease entity (Mol et al., 2016; Roberts et al., 2013; Sibai et al., 2005; Steegers et al., 2010). Therefore, we performed four sets of meta-analysis: for the association between air pollution and four complications of pregnancy (GDM, GH, preeclampsia/eclampsia, and HDP (including GH and preeclampsia)) in different exposure window groups. We conducted meta-analysis for continuous exposure. We assumed ORs approximate RRs since the prevalence of pregnancy complications in study populations was low. The reported RRs and their 95% CIs were converted to corresponding common exposure increments (5 $\mu g/m^3$ $PM_{2.5}$, 10 $\mu g/m^3$ PM_{10}, 0.1 part per million (ppm) CO, 1 part per billion (ppb) NO, 10 $\mu g/m^3$ NO_2, 10 ppb NO_x, 10 ppb O_3, 1 ppb SO_2). The following formula was used to calculate standardized risk estimates:

$$RR_{standardized} = RR_{origin}^{\left(\frac{increment_{standardized}}{increment_{origin}}\right)}$$

We conducted meta-analysis if at least three studies reported the association between the same pollutants and disease in the same exposure window group. We used the combined estimates from the adjusted and single-pollutant models in each included study. In addition, there were three studies (Mendola et al., 2016; Savitz et al., 2015; Wu et al., 2011), which reported their results in two separate groups. Wu et al. (2011) reported risk estimates separately based on two study locations in the USA (Los Angeles County and Orange County) due to their remarkably different socio-demographic characteristics and the land use regression models were originally based on measurements in Los Angeles Country only. Savitz et al. (2015) separated the preeclampsia group into mild preeclampsia and severe preeclampsia/eclampsia group and reported the results separately. Mendola et al. (2016) aimed to examine whether the relationships between preeclampsia and air pollution were different among women with and without asthma and presented their results based on these two groups. Given above reasons, we treated each of the three articles as two different articles.

The pooled RRs and their 95% CIs were calculated using the inverse variance method and the *Z* test was applied to test the significance of the pooled results. The heterogeneity between studies was evaluated using I^2 statistics. If I^2 was less than 50%, it indicated that there was moderate or low heterogeneity between studies and fixed effect model was adopted. Otherwise, a random effect model was applied ($I^2 \geq 50\%$) (Liu et al., 2019). Publication bias was evaluated by funnel plots and Egger tests, and *p*-values of Egger tests less than 0.05 showed there was publication bias. All the above analyses were performed using the package "metan" of STATA software (Version 15, StataCorp, College Station, Texas, USA).

3. Results

3.1. Literature search and study characteristics

Through the four databases searching, we identified 10,378 records in total. After excluding duplicates and other literatures according to the eligibility assessment by titles and abstracts, 86 articles were retrieved for full-text review. Ultimately, 33 cohort studies were eligible for this meta-analysis based on the inclusion and exclusion criteria (Fig. 1).

Table 1 presents the characteristics of individual studies included in this meta-analysis. This study was based on 2093 to 17,783,269 pregnancies occurring during 1996–2018, and a total of 22,253,277 women were included from the 33 cohort studies. 21 studies were conducted in the United States, 4 in China, 1 in Netherlands, 1in Canada, 1 in Spain, 2 in Sweden, 1 in Australia, and 2 in Denmark. Twelve studies explored the association between air pollution exposure and GDM, nine evaluated HDP with a combination of GH and preeclampsia, nine considered GH, and sixteen evaluated preeclampsia. Adjusted covariates were different among studies and detailed information is shown in Table 1. NOS scores of quality assessment showed that 27 studies (82%) were classified as "high quality" (Table 1).

3.2. Gestational diabetes mellitus

In this present meta-analysis, the total cases of GDM in the included twelve studies were 93458 and the prevalence of GDM ranged from 0.289% to 21.383%. Nine cohort studies examined the effect of $PM_{2.5}$ on GDM based on different exposure windows, and the random-effect model was applied to analyze the overall effect with I^2 more than 50%. During the first and second trimester, we found that GDM was not significantly associated with a 5 μg/m^3 increment in $PM_{2.5}$ (RR = 1.02, 95% CI: 0.97–1.07, first trimester; RR = 1.06, 95% CI: 0.98–1.14, second trimester) (Table 2). We also meta-analyzed four studies investigating the risk for developing GDM in relation to SO_2 during the first trimester and found that pooled effect was 1.04 (95% CI: 1.00–1.08, per 1 ppb increment) (Table 3). The associations of GDM with PM_{10}, CO, O_3, and NO_2 were not observed in this present meta-analysis. Detailed information was presented in Table 2 and supplementary file (Table S1).

3.3. Hypertensive disorders of pregnancy

For hypertensive disorders of pregnancy, we extracted data on $PM_{2.5}$, PM_{10}, and NO_2. There were not enough articles or no reports on other pollutants, therefore, we only conducted meta-analysis on these three pollutants. Random-effect model was applied to combine data. Among the nine studies that reported the association between HDP and ambient air pollution, the prevalence of HDP ranged from 2.600% to 5.425% and there were 585,752 cases in total. The overall estimates for developing hypertensive disorders of pregnancy were 1.02 (95%: 0.91–1.13), 1.01 (95% CI: 0.93–1.09), and 1.18 (95% CI: 1.02–1.34) for an increment of 5 μg/m^3 $PM_{2.5}$ during the first trimester, the second trimester and the entire pregnancy, respectively (Table 2). We only analyzed data on PM_{10} during the entire pregnancy due to insufficient data in other exposure windows, and we observed that there was no significant association between PM_{10} and hypertensive disorders of pregnancy (RR = 0.99, 95% CI: 0.97–1.00, per 10 μg/m^3 increment) (Table 2). In addition, we extracted data on NO_2 from three articles (Table S1), and after we combined the risk estimates from these studies, we found that a 10 μg/m^3 increment in NO_2 was not associated with hypertensive disorders of pregnancy (RR = 1.04, 95% CI: 0.94–1.14).

3.4. Preeclampsia

Sixteen articles discussed the association of ambient air pollution with preeclampsia. There were 40,989 cases among them, and the prevalence of preeclampsia ranged from 1.226% to 4.609%. Seven included articles (including 10 studies) explored the risk for developing preeclampsia in relation to $PM_{2.5}$ during the first trimester, and the combined risk estimate was 0.97 (95% CI: 0.95–0.99, per 5 μg/m^3 increment) using the fixed-effect model (I^2 = 4.1%). For the other two exposure windows (the entire pregnancy and the second trimester), this association was not observed. We also analyzed the association between preeclampsia and PM_{10} during the first trimester, the second trimester, and the entire pregnancy. The heterogeneity between studies was low with I^2 of 22.3%, 0%, and 0%, respectively, therefore, a fixed-effect model was used to combine RRs. The corresponding effect estimates were 1.01 (95% CI: 0.98–1.05, per 10 μg/m^3 increment), 1.01 (0.97–1.05, per 10 μg/m^3 increment), and 1.03 (95% CI: 0.98–1.08, per 10 μg/m^3 increment), respectively (Table 2). In terms of remaining pollutants (CO, NO_2, NO_X, O_3, SO_2), we conducted meta-analysis during different exposure windows except the third trimester due to limited studies, and no significant associations were observed in these meta-analyses (Table 3, Table S1).

3.5. Gestational hypertension

There were 40059 cases in total among the nine studies reporting the effect risks of air pollutants for developing gestational hypertension, and the prevalence of gestational hypertension ranged from 1.052% to 5.988%. Four studies reported the association between PM_{10} and preeclampsia during the first trimester, including 299,111 pregnancies with 10266 cases. We observed a significant association between them (RR = 1.07, 95% CI: 1.02–1.12, per 10μg/m3 increment) using the fixed-effect model with I^2 of 0.0% (Table 2). During the entire pregnancy, the combined risk estimate was 1.11(95% CI: 0.90–1.32, per 10μg/m3 increment). Five articles explored the association of $PM_{2.5}$ with gestational hypertension during the first trimester and four articles

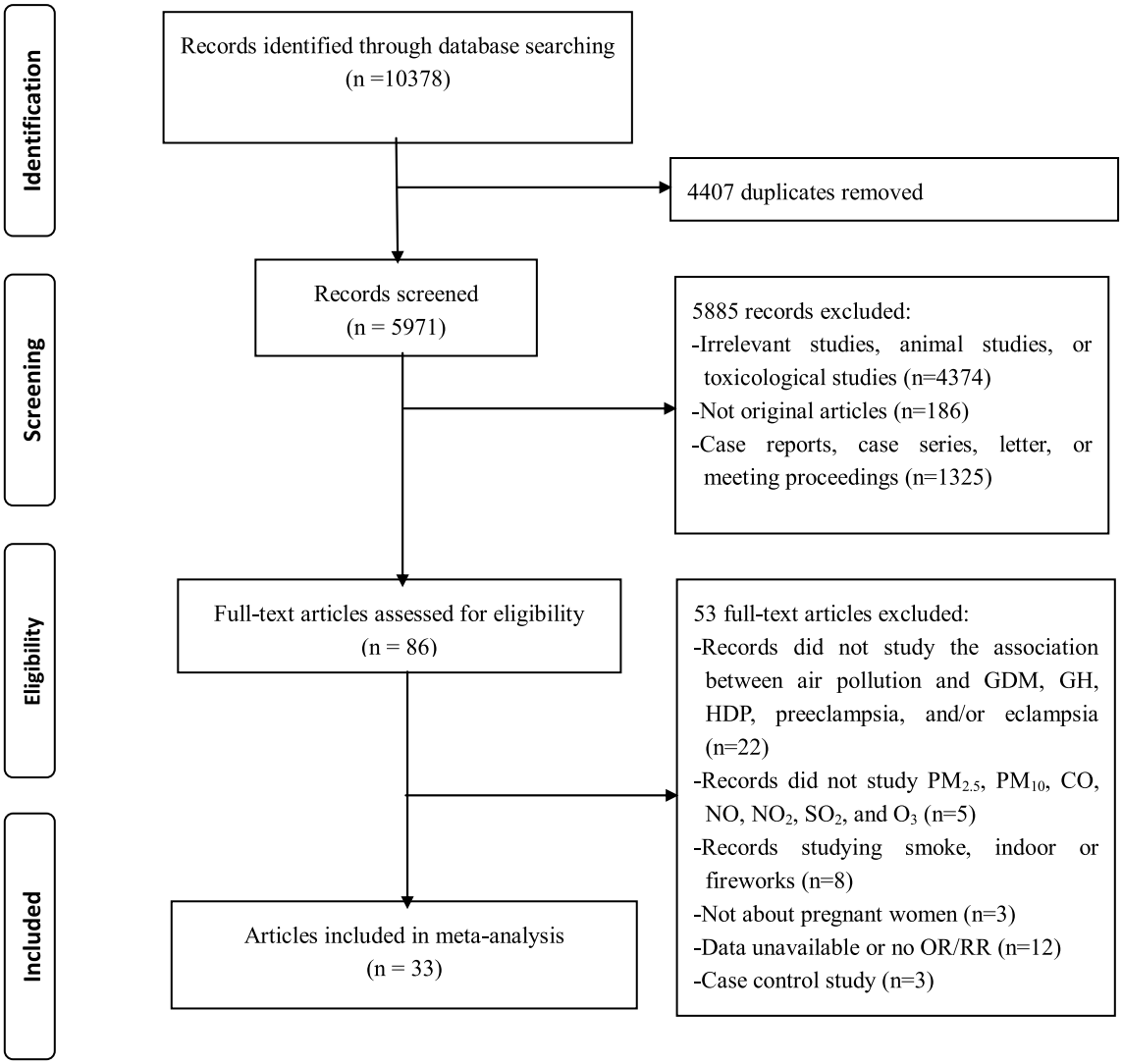

Fig. 1. Flow diagram of literature search for meta-analysis.

discussed the association during the second trimester. After calculating the combined estimates using the random-effect model, there was no significant association between them (Table 2). Additionally, for pollutants NO_2 and SO_2, meta-analysis was applied during the first trimester and no significant association was observed (Table 3, Table S1).

3.6. Publication bias

We conducted 40 meta-analyses and funnel plots for each pollutant related to different gestational diseases during each exposure window were drawn (Figures not shown). Egger tests were applied to examine publication bias, and significant *p*-values were found for only 2 of the 40 meta-analyses we carried out (Table S1), which indicated that wide-scale publication bias was unlikely.

4. Discussion

This systematic review and meta-analysis summarized the evidence from a large number of cohort studies regarding the association between ambient air pollution and pregnancy complications (including gestational diabetes mellitus, hypertensive disorders of pregnancy, gestational hypertension, and preeclampsia) in different exposure windows. During the first trimester, exposure to $PM_{2.5}$, PM_{10}, and SO_2 was associated with preeclampsia, gestational hypertension, and gestational diabetes mellitus, respectively. This exposure window may be a sensitive period during pregnancy and should be noticeable. Additionally, $PM_{2.5}$ significantly increased the risk of hypertensive disorders of pregnancy during the entire pregnancy. We found no significantly increased risk of other ambient air pollutants in relation to pregnancy complications.

There is increasing evidence supporting that pregnant women may be more sensitive to air pollution in their early pregnancy. Lee et al. (2013) hypothesized that maternal vascular remodeling processes in early pregnancy (i.e., first trimester) may be interfered by exposure to air pollutants and Dinh et al. (2014) suggested that impaired vasodilation was associated with endothelial dysfunction. Several studies (Rajagopalan and Brook, 2012; Rao et al., 2015) report that biological pathways, including insulin resistance, endothelial dysfunction and systemic inflammation, may link ambient air pollution to type 2 diabetes. The epidemiological data (Ben-Haroush et al., 2004) suggest an association between GDM and type 2 diabetes by insulin resistance as a pathogenic linkage, and a meta-analysis (Bellamy et al., 2009) reports that women with GDM have at least a seven-fold increased risk of developing type 2 diabetes in the future compared with pregnancies without GDM. Therefore, we hypothesize that GDM may share similar pathophysiology processes to type 2 diabetes and it may also be associated with ambient air pollution. In this present meta-analysis, we find that SO_2 exposure increases the risk of GDM during the first trimester.

Table 1
Basic characteristics of included studies.

Reference[a]	Duration of data collection	Design	Location	Sample size	Pollutant	Outcome[b] (number of cases)	Covariates	NOS scores
Wu et al., 2009	1997–2006	Hospital-based cohort	USA	81,186	NO_X, $PM_{2.5}$	PE (2442)	Maternal age, maternal race/ethnicity, parity, prenatal care insurance type, poverty, and season of conception	8
Rudra et al., 2011	1996–2006	Hospital-based cohort	USA	3509	CO, $PM_{2.5}$	PE (117)	Age, race/ethnicity, pre-pregnancy BMI, smoking history, and season of conception	8
Van den Hooven et al., 2011	2001–2005	Register-based cohort	Netherlands	7006	NO_2, PM_{10}	GH (250), PE (141)	Maternal age, height, weight at enrollment, parity, ethnicity, education, folic acid supplementation, smoking, alcohol consumption, and noise exposure	7
Wu et al. (2011)	1997–2006	Hospital-based cohort	USA	81,186	CO, NO, NO_2, NO_X, O_3, PM_{10}, $PM_{2.5}$	PE (1303 + 1139)	Maternal age, maternal race/ethnicity, parity, diabetes, prenatal care, insurance type, poverty, season of conception, and diabetes	8
Vinikoor-Imler et al., 2012	2000–2003	Register-based cohort	USA	222,775	$PM_{2.5}$, PM_{10}	HDP (12085)	Neighborhood deprivation index, maternal age, maternal education, smoked during pregnancy, previous birth, race, and marital status	6
Zhai et al., 2012	2004–2009	Register-based cohort	Canada	121,158	CO	PE (2097)	Maternal age, parity, smoking, previous cesarean section delivery, maternal health problem (chronic hypertension, types 1 and 2 diabetes mellitus, heart disease), income, and education	8
Dadvand et al. (2013)	2000–2005	Hospital-based cohort	Spain	8398	NO_X, NO_2, $PM_{2.5}$, PM_{10}	PE (103)	Neighborhood socioeconomic status, ethnic origin, education level, marital status, age, smoking, alcohol consumption, body mass index, diabetes, parity, multiple pregnancy, season of conception, and year of conception	7
Lee et al. (2013)	1997–2002	Hospital-based cohort	USA	34,705	PM_{10}, $PM_{2.5}$, O_3	GH (2078), PE (1141)	Maternal age, race, parity, number of cigarettes smoked during pregnancy, season of birth, and year of conception	7
Olsson et al. (2013)	1998–2006	Register-based cohort	Sweden	120,755	O_3, NO_X	PE (3260)	Maternal age, parity, level of education, area of origin, maternal asthma, season of conception, and conception year	8
Pereira et al., 2013	2000–2006	Register-based cohort	Western Australia	23,452	NO_2	PE (943)	Maternal age, diabetes, aboriginal status, parity, season of conception, maternal smoking during pregnancy and the socioeconomic index for areas (SEIFA) score	7
Fleisch et al., 2014	1999–2002	Register-based cohort	USA	2093	$PM_{2.5}$	GDM (118)	Age, pre-pregnancy BMI, pregnancy weight gain, education, race/ethnicity, family history of diabetes, prior GDM, and season of last menstrual period	6
Xu et al., 2014	2004–2005	Register-based cohort	USA	22,041	NO_2, $PM_{2.5}$, SO_2, CO, O_3	HDP (1037)	Maternal age, race, education, marital status, smoking during pregnancy, season of conception, year of conception, prenatal care began and tract median household income	8
Hu et al., 2015	2004–2005	Register-based cohort	USA	410,267	$PM_{2.5}$, O_3	GDM (14032)	Maternal age, race, education, marital status, season of conception, year of conception, prenatal care began, urbanization, and median household income	8
Huang et al., 2015	2010–2012	Hospital-based cohort	China	8745	PM_{10}	HDP (333), GH (127), PE (206)	Maternal age, education, income per capita, prenatal BMI, parity, folic acid intakes, previous PIH, conception season, and average temperature in corresponding time periods.	6
Olsson et al., 2015	1997–2006	Register-based cohort	Sweden	74,991	NO_X	HDP (1950)	Maternal asthma, maternal level of education, maternal area of origin, maternal age, first trimester temperature, first trimester ozone, day and year of conception, maternal smoking, body mass index, and family situation.	7
Robledo et al., 2015	2002–2008	Hospital-based cohort	USA	219,952	PM_{10}, $PM_{2.5}$, NO_X, SO_2, O_3, CO	GDM (11334)	Maternal age, race and study site	8
Savitz et al. (2015)	2008–2010	Hospital-based cohort	USA	348,585	NO_2, $PM_{2.5}$	HDP (17000), GH (5834), PE (6940 + 4226)	Maternal age, maternal ethnicity, maternal education, Medicaid status, parity, conception year, deprivation index, BMI, BMI2, hospital	8
Fleisch et al., 2016	2003–2008	Register-based cohort	USA	159,373	$PM_{2.5}$	GDM (5381)	Maternal characteristics (age, race/ethnicity, education, prenatal insurance, smoking habits), census tract characteristics (median household income, percent open space, and median value of owner-occupied housing),	8
Mendola et al. (2016)	2002–2008	Hospital-based cohort	USA	228,438	PM_{10}, $PM_{2.5}$, NO_X, SO_2, O_3, CO	PE (918 + 9610)	Maternal race/ethnicity, age, parity, pre-pregnancy BMI, smoking and alcohol use, insurance status, marital status and study site. The estimates are based on the interaction of maternal asthma and each pollutant derived from a single model, not stratified analyses.	7

(*continued on next page*)

Table 1 (*continued*)

Reference[a]	Duration of data collection	Design	Location	Sample size	Pollutant	Outcome[b] (number of cases)	Covariates	NOS scores
Hu et al., 2017	2005–2007	Register-based cohort	USA	655,529	O_3	HDP (31326)	Maternal age, race, education, marital status, pregnancy smoking status, pre-pregnancy BMI, season of conception, and year of conception.	8
Pan et al., 2017	2004–2005	Register-based cohort	China	21,248	PM_{10}, CO, NO, NO_2, NO_X, SO_2, O_3	GDM (378)	Maternal age, BMI, weight gain, fetal gender, parity and annual household income.	6
Pedersen et al., 2017a	1997–2002	Register-based cohort	Danish	72,745	NO_2	HDP (2340), GH (765), PE (1880)	Maternal age, parity, pre-pregnancy BMI, height, disposable income, education, and season of conception.	8
Pedersen et al., 2017b	1997–2002	Register-based cohort	Danish	72,745	NO_2	GDM (210)	Maternal age, parity, pre-pregnancy BMI, height, disposable income, education, and season of conception.	8
Zhu et al., 2017	2002–2008	Hospital-based cohort	USA	206,054	CO, NO_X, O_3, SO_2, PM_{10}, $PM_{2.5}$	GH (6074)	Study site, maternal age, race/ethnicity, marital status, insurance, parity, pre-pregnancy body mass index during pregnancy, season of conception. preexisting chronic disease, smoking during pregnancy, and alcohol consumption	7
Choe et al., 2018	2002–2012	Hospital-based cohort	USA	61,640	$PM_{2.5}$	GDM (4884), GH (2877), PE (2221)	Mother's age, tobacco use, parity, education, race, insurance, marital status, NSES z-score, year of last menstrual period, and conditional on town of residence (39 towns total).	8
Madsen et al., 2018	2001–2009	Register-based cohort	USA	17,533	NO_2	HDP (941), PE (590)	Maternal age, BMI, diabetes, chronic hypertension, maternal education, maternal marital status, parity, smoking during pregnancy, birth season, area, year of birth.	7
Xue et al., 2018	1999–2004	Register-based cohort	USA	17,783,269	PM2.5, PM10	HDP (518740)	Infant sex, maternal age, maternal race, marital status, maternal education attainment, maternal tobacco consumption during pregnancy, maternal alcohol consumption during pregnancy, prenatal care, parity, delivery method, maternal diabetes mellitus, county-level poverty, maternal weight gain during pregnancy, temperature, year index, season index, and state index.	8
Abdo et al. (2019)	2007–2015	Register-based cohort	USA	535,895	$PM_{2.5}$	GDM (20178), GH (20067)	Ozone, non-wildfire PM2.5, PM10, temperature deviation, calendar month, year, mother's race/ethnicity, mother's education, income, mother's age, smoking during pregnancy, drinking during pregnancy, asthma, gestational age, and graduated index	6
Choe et al., 2019	2008–2010	Hospital-based cohort	USA	348,585	$PM_{2.5}$, NO_2	GDM (17065)	Maternal age, maternal ethnicity, maternal education, Medicaid status, parity, working during pregnancy, deprivation index, BMI, and conception year, conditional on zip code, other pollutant in the same trimester, the same pollutant in the other trimester, and season of conception	8
Jo et al. (2019)	1999–2009	Register-based cohort	USA	239,574	PM_{10}, $PM_{2.5}$, NO_2, SO_2	GDM (18244)	Family correlation, birth year, KPSC medical center service areas, maternal age, race/ethnicity, education, household income, parity	8
Nobles et al. (2019)	2002–2010	Register-based cohort	USA	49,607	PM_{10}, $PM_{2.5}$, NO_X, NO_2, SO_2, O_3, CO	GH (1987), PE (1712)	Maternal age, race/ethnicity, pre-pregnancy body mass index, smoking, alcohol use, parity, insurance type, marital status, history of asthma, and temperature.	8
Yao et al., 2019	2015–2018	Hospital-based cohort	China	4817	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO	GDM (1030)	Maternal age, maternal education, pre-pregnancy body mass index, husband alcohol drinking, parity, frequency of fruits intake, frequency of dessert intake, physical activity for the last three months, the status of diabetes in the immediate family, the season of glucose tolerance test	5
Zhang et al., 2019	2011–2014	Hospital-based cohort	China	5421	$PM_{2.5}$, PM_{10}, SO_2, NO_2	GDM (604)	Maternal age, pre-pregnancy BMI, maternal education level, family income, infant gender, maternal tobacco smoking, passive tobacco smoking, maternal alcohol consumption, parity, season of conception	7

Note.

[b] In Wu et al., 2011 study, the cases of preeclampsia were 1303 in the Los Angeles Country and 1139 in the Orange Country; In Savitz et al., 2015 study, the cases of mild preeclampsia were 6940, and severe preeclampsia/eclampsia were 4226; In Mendola et al., 2016 study, 918 preeclampsia cases were with asthma and 9610 without asthma.

[a] The corresponding studies were presented in the reference list in the supplementary file.

Table 2
Summary of meta-analysis of studies on maternal exposure to particulate matter and pregnancy complications.

Pollutants[a]	Exposure time	Included studies[b]	Total number of cases	Sample size	Relative risk (95% CI)	I^2	*P*-values of Egger test
$PM_{2.5}$	*Outcome: GDM*						
	Entire pregnancy	13,28	34210	946162	–	–	–
	First trimester	13,16,18,25,28,29,30,32,33	92752	1985524	1.02(0.97–1.07)	86.0%	0.256
	Second trimester	11,13,18,25,28,29,33	62262	1523274	1.06(0.98–1.14)	72.7%	0.173
	Third trimester	28	20178	535895	–	–	–
	Outcome: HDP						
	Entire pregnancy	**5,12,27**	**531862**	**18028085**	**1.18(1.02–1.34)**	**85.1%**	**0.185**
	First trimester	12,17,27	536777	18153895	1.01(0.93–1.09)	87.4%	0.915
	Second trimester	12,17,27	536777	18153895	1.02(0.91–1.13)	93.6%	0.983
	Third trimester	27	518740	17783269	–	–	–
	Outcome: PE						
	Entire	1,2,4a,4b,7,19a,19b,31	17344	402717	1.08(0.97–1.18)	71.3%	0.249
	First trimester	**4a,4b,7,8,17a,17b,19a,19b,25,31**	**29313**	**762952**	**0.97(0.95–1.00)**	**4.1%**	**0.228**
	Second trimester	4a,4b,7,17a,17b,19a,19b,25,31	28172	728247	0.98(0.96–1.01)	0.0%	0.341
	Third trimester	7,25	2324	70038	–	–	–
	Outcome: GH						
	Entire pregnancy	28,31	22054	535895	–	–	–
	First trimester	8,17,24,25.28,31	38917	1186879	1.05(0.98–1.12)	63.1%	0.188
	Second trimester	17,25,28,31	30765	946120	1.01(0.96–1.06)	82.4%	0.315
	Third trimester	25,28	22944	597535	–	–	–
PM_{10}	*Outcome: GDM*						
	First trimester	16,21,30,32,33	31590	491012	0.99(0.97–1.00)	0.0%	0.512
	Second trimester	21,33	982	26669	–	–	–
	Third trimester	21	378	21248	–	–	–
	Outcome: HDP						
	Entire pregnancy	5,14,27	531158	18014789	1.08(0.97–1.20)	85.8%	0.281
	First trimester	14,27	519073	17792014	–	–	–
	Second trimester	27	518740	17783269	–	–	–
	Third trimester	27	518740	17783269	–	–	–
	Outcome: PE						
	Entire pregnancy	3,4a,4b,7,14,19a,19b,31	15132	333773	1.03(0.98–1.08)	22.3%	0.650
	First trimester	4a,4b,7,8,14,19a,19b,31	16132	361472	1.01(0.98–1.05)	0.0%	0.341
	Second trimester	4a,4b,7,19a,19b,31	14785	318022	1.01(0.97–1.05)	0.0%	0.224
	Third trimester	7	103	8398	–	–	–
	Outcome: GH						
	Entire pregnancy	3,14,31	2364	15751	1.11(0.90–1.32)	74.6%	0.753
	First trimester	**8,14,24,31**	**10266**	**249504**	**1.07(1.02–1.12)**	**0.0%**	**0.434**
	Second trimester	31	1987	49,607	–	–	–

Note.
The significant associations were shown in bold.
[a] The corresponding exposure increments were 5 μg/m^3, $PM_{2.5}$ and 10 μg/m^3, PM_{10}, respectively.
[b] The corresponding numbering of included studies was presented in the reference list in the supplementary file.

Table 3
Summary of meta-analysis of studies on maternal exposure to SO_2 and pregnancy complications.

Exposure time	Included studies[a]	Total number of cases	Sample size	Relative risk (95% CI)	I^2	*P*-values of Egger test
Outcome: GDM				–	–	–
First trimester	**16,21,32,33**	**13346**	**251438**	**1.04(1.00–1.08)**	**54.1%**	**0.003**
Second trimester	21,33	982	26669	–	–	–
Third trimester	21	378	21248	–	–	–
Outcome: HDP						
Entire pregnancy	12	1037	22041	–	–	–
First trimester	12	1037	22041	–	–	–
Second trimester	12	1037	22041	–	–	–
Outcome: PE						
Entire pregnancy	19a,19b,31	12240	228438	1.01(0.98–1.04)	51.1%	0.179
First trimester	19a,19b,31	12240	228438	1.00(0.97–1.03)	71.7%	0.179
Second trimester	19a,19b,31	12240	228438	1.01(0.99–1.04)	60.6%	0.017
Outcome: GH						
Entire pregnancy	31	1987	49,607	–	–	–
First trimester	8,24,31	10139	240759	1.03(0.99–1.08)	83.2%	0.469
Second trimester	31	1987	49,607	–	–	–

Note.
The significant associations were shown in bold; The corresponding exposure increment was 1 part per billion (ppb) for SO_2.
[a] The corresponding numbering of included studies was presented in the reference list in the supplementary file.

However, the potential underlying mechanisms have not been reported by any publications and it is worth in-depth study in future research.

Similarly, the mechanisms mentioned above can also explain that air pollution can aggregate the development and progression of atherosclerosis (Allen et al., 2012; Campen et al., 2012), contributing to hypertension. HDP and atherosclerotic cardiovascular diseases may share pathways due to their similarities, therefore, the underlying mechanisms (inflammation, oxidative stress, and endothelial dysfunction) of latter in relation to air pollutants can also apply to HDP (Brook, 2008). In our present meta-analysis, we found that exposure to $PM_{2.5}$ was associated with HDP and preeclampsia. It should be noted that we found a negative relation between $PM_{2.5}$ and preeclampsia, which is different from our previous cognition. A meta-analysis (Wei et al., 2015) found that there was a significant negative association between smoking during pregnancy and incidence of preeclampsia. This indicated that our results may be related to why we see an inverse relationship between smoking and preeclampsia. However, the combined risk effect is 0.97 (95% CI: 0.95–1.00), which approaches to 1, therefore, we should take caution when interpreting the result above. In addition, our results indicate that PM_{10} increases the risk of gestational hypertension during the first trimester. A meta-analysis (last search: December, 2013) (Pedersen et al., 2014) explored the association between exposure to ambient air pollution and pregnancy-induced hypertensive disorders and found that PM_{10} increased the risk of HDP during the entire pregnancy. Due to insufficient number of literatures at that time, they do not analyze gestational hypertension as a separate outcome and focus solely on one exposure window. Another meta-analysis (last search: September 2013) (Hu et al., 2014), which included both cohort and case-control studies, also investigated the effect of PM_{10} on HDP (including gestational hypertension and preeclampsia) and preeclampsia, and no significant associations were observed during different exposure windows (full gestational period, first trimester and second trimester). A highlight in our present meta-analysis is that we analyze air pollution in relation to HDP (including GH, preeclampsia/eclampsia), GH, and preeclampsia, respectively. Though there are only four studies exploring the relationship between PM_{10} and GH during the first trimester, these studies are all large cohort studies with at least 8000 pregnancies in each study and they can provide a relatively robust result.

Heterogeneity in this meta-analysis should be noticed because among the 40 meta-analyses, most of them are with heterogeneity. We extracted adjusted relative risks from included studies, and the heterogeneity of our findings may be a consequence of confounding factors with varying degrees of control. Most studies set maternal age, maternal ethnicity, parity, pregnancy body mass index, maternal education, smoking, and diabetes as covariates (Table 1), however, studies that lacked above information may fail to adjust these factors when analyzing the association between air pollutants and pregnancy complications. The level of ambient air pollution various in different regions, such as in the rural and urban areas, or in the developing and developed countries. It is well known that seasonal variation can affect the level of air pollution. We also noticed that it may influence the risk estimate after the adjustment for other air pollutants (Pedersen et al., 2013) and traffic-related noise (Gehring et al., 2014). These above factors are always overlooked and not assessed, which may be the source of heterogeneity. In addition, the heterogeneity might be related to the exposure assessment in the studies. There are various ways of exposure measurement method among included studies, including using monitored air pollution data (Olsson et al., 2013), land use regression (LUR) model (Dadvand et al., 2013), and dispersion model (Wu et al., 2011). Hu et al. (2014) suggested that different outcomes used in individual studies may cause heterogeneity, and encouraged to analyze GH and preeclampsia separately. Therefore, we found some significant associations with low heterogeneity when only analyzing GH or preeclampsia. Though low heterogeneity was observed to some extent, there were inevitable sources of heterogeneity and we failed to conduct subgroup analysis due to limited studies after grouping studies.

There are several strengths in our study. Meta-analysis can provide a more precise finding and increase the statistical power for rare outcomes compared with the results from individual articles. To provide a high-quality result of evidence-based medicine, we only included cohort studies and provided prevalence of different pregnancy complications. All the included cohort studies consist of at least 8000 participants, so, there is no significant evidence of small study bias, such as publication bias, in our study. Additionally, we for the first time separated HDP into GH and preeclampsia, and discussed the risk of exposure to various ambient air pollutants on GDM, HDP, GH, and preeclampsia, respectively, during different exposure windows. Our study has a few limitations that should not be ignored. We focus on four exposure windows in our study and there are original articles reporting preconception pregnancy air pollution exposure, however, we fail to conduct meta-analysis due to limited data. Additionally, we analyzed the risk of common air pollutants on pregnancy complications, but there were a few papers exploring the constituents of pollutants. Though we cannot conduct meta-analysis because of insufficient studies, we believe these studies will be useful to discuss the mechanisms of effects of pollutants on diseases.

This meta-analysis suggests an association between ambient air pollution and pregnancy complications especially during the first trimester. Further large multicenter cohort studies that consider more factors, such as traffic-related noise, other air pollutants, and nutrition status, are recommended. More studies on different constituents of pollutants and mixtures of air pollutants, levels of disease severity, mechanisms of exposures' impact on HDP and GDM, sensitive populations (i.e. pregnant women with asthma) and various exposure windows, especially during preconception, are warranted in the future research.

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Declaration of competing interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.109471.

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