

Review Article

Association between atmospheric particulate matter and adverse pregnancy outcomes in the population

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Received April 13, 2016; Accepted September 22, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: This systematic review and meta-analysis was conducted to assess the association between maternal exposure to the level of atmospheric particulate matter (PM) during pregnancy and adverse pregnancy outcomes for different exposure pregnancy trimesters. Among a total of 671 identified articles, 43 were reviewed in depth, of which only 18 satisfied the inclusion criteria. The positive associations were identified between Small for gestational age (SGA) and maternal exposure to PM_{2.5} in the first (OR = 1.074, 95% CI = 1.046-1.103), the second (OR = 1.058, 95% CI = 1.019-1.100), the third (OR = 1.062, 95% CI = 1.042-1.083) trimesters and the entire pregnancy period (OR = 1.151, 95% CI = 1.104-1.200), which indicated that with every 10 µg/m³ increase in PM_{2.5}, the risk of SGA would increase 7.4%, 5.8%, 6.2% and 15.1%, respectively. The occurrence of SAB was significantly positive with a 10 µg/m³ increase in PM₁₀ (OR = 1.340, 95% CI = 1.043-1.721), indicating an 34% increased risk of SAB. There were no statistically significant associations were observed between stillbirth and maternal exposure to PM in three trimesters. In conclusion, it might be a wise practice for pregnant women to take effective measures to reduce PM exposure.

Keywords: Meta-analysis, PM, pregnancy outcomes, SAB, SGA, stillbirth

Introduction

A fetus is particularly sensitive to environment, since environment pollutants could have a deleterious impact on fetal development and growth by disturbing the function of placenta or causing direct damage on the processes of high cell proliferation, differentiation, and rapid organ development [1]. Adverse pregnancy outcomes are abnormal results of fetal growth and development, including spontaneous abortion (SAB), stillbirth, small for gestational age (SGA), low birth weight (LBW), preterm delivery (PTD) and birth defects, etc. [2]. Adverse pregnancy outcomes are considered as important factors of fetal mortality, and they are also well known as big threats to neonatal health [3]. Poor pregnancy outcomes, which depend on a complex combination of genetic, social, and environmental factors, also bring a heavy psychological and economic burden to both family and society [4].

In the past few years, air pollution has become a major public health issue raising concerns around the world. Maternal exposure to ambient air pollution has been suggested as a risk factor for adverse birth outcomes [5, 6]. For their small sizes, PM_{2.5} and PM₁₀ (fine particulate matter with aerodynamic diameter less than 2.5 µm and less than 10 µm respectively) could easily enter the depths of maternal respiratory tract and participate in blood circulation [2], eliciting a wide range of biological responses. They can also affect pregnant women in their cardiovascular system and general health condition through hindering the input of glucose, oxygen and insulin. Oxidative stress and inflammation or others could be the mechanistic pathways by which exposure to the pollutant may result in onset of low birth weight, preterm, or other adverse pregnancy outcomes [7]. Maternal exposure to transition metal contained in PM could lead to oxidative stress that

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Table 1. Contextual details of studies included in the meta-analysis

First Author, Publication year	Country	Study period	Study design	Sample size	PM	Outcomes	Exposure period	Adjustment
Brauer, 2008	Vancouver, Canada	1999-2002	Retrospective cohort	70,249	PM2.5	SGA	Entire pregnancy	Tobacco and alcohol use during pregnancy, first nations status, parity, mothers marital status, and others
Gray, 2014	North Carolina, USA	2002-2009	Cross-sectional study	457,642	PM2.5	SGA	Entire pregnancy, trimester	Marital status, tobacco use during pregnancy, alcohol use during education, race, age, and others
Hannam, 2014	Northwest England	2004-2008	Retrospective cohort	203,562	PM2.5	SGA	Entire pregnancy, trimester	Maternal education, ethnicity, tobacco use during pregnancy, and others
Hyder, 2014	Massachusetts and Connecticut, USA	2000-2006	Cross-sectional study	628,131	PM2.5	SGA	Entire pregnancy, trimester	Maternal age, prenatal care, educational attainment parity, infants sex, and others
Lee, 2013	Pittsburgh, PA USA	1997-2002	Retrospective cohort	34,705	PM2.5	SGA	1st trimester	Maternal age, race, parity, number of cigarettes smoked during pregnancy, and others
Liu, 2007	Canadian	1985-2000	Cross-sectional study	386,202	PM2.5	IUGR	Trimester	Maternal age, parity, infant sex, season of birth, and residence of city
Mannes, 2005	Sydney, Australia	1998-2000	Cross-sectional study	138,056	PM2.5	SGA	Entire pregnancy, trimester	Maternal age, education, ethnicity, and parity smoking during pregnancy, and others
Parker, 2005	California, USA	2000	Cross-sectional study	18,247	PM2.5	SGA	Entire pregnancy	Marital status, tobacco use during pregnancy, alcohol use during education, race, age, and others
Rich, 2009	New Jersey, USA	1999-2003	Retrospective cohort	350,107	PM2.5	SGA	Trimester	Maternal race, age, maternal education, marital status, trimester prenatal care began and others
Green, 2015	California, USA	1999-2009	Retrospective cohort	3026269	PM2.5	Stillbirth	Entire pregnancy, trimester	Infant sex, maternal demographic characteristics, season of last menstrual period, apparent temperature, air basin of mother's residence, and year of conception
Faiz, 2012	New Jersey, USA	1998-2004	Retrospective cohort	222734	PM2.5	Stillbirth	Entire pregnancy, trimester	Maternal age, maternal race/ethnicity, maternal educational level, prenatal care initiation, neighborhood index, indicator variables for calendar month and year of the date of conception and mean apparent temperature during the first trimester, self-reported smoking
Pearce, 2009	Newcastle upon Tyne, England	1962-1992	Retrospective cohort	91349	PM4	Stillbirth	Entire pregnancy, trimester	Infant sex, maternal age, parity and Townsend deprivation score
DeFranco, 2015	Ohio, USA	2006-2010	Retrospective cohort	351036	PM2.5	Stillbirth	Entire pregnancy, trimester	Maternal age, race, education level, quantity of prenatal care, smoking, and season of conception
Kim, 2007	Seoul, Korean	2001-2004	Retrospective cohort	1514	PM10	Stillbirth	Trimester	Infant sex, infant order, maternal age, and education level, paternal education level, season of birth, alcohol drinking, maternal body mass index (BMI), and maternal weight just before delivery
Hwang, 2011	Taiwan, China	2001-2007	Case-control study	102575	PM10	Stillbirth	Entire pregnancy, trimester	Maternal age, sex of the infant, and season of conception, municipal-level socioeconomic status
Perin, 2010	São Paulo, Brazil	1997-2006	Retrospective cohort	640	PM10	SAB	14 days following LMP	Year of IVF treatment and age
Ciaula, 2014	Apulia, Southern Italy	2013	Cross-sectional study	514996	PM10	SAB	1st trimester	Weather
Moridi, 2014	Tehran, Iran	2010-2011	Case-control study	296	PM10	SAB	1st trimester	Maternal age, husband age, gravidity, duration from last delivery in multiparous women, history of previous abortion, pre-pregnancy body mass index (BMI), occupation, educational status, second-hand smoke exposure, socioeconomic status, consanguinity with the spouse and duration of residence in Tehran

SAB: spontaneous abortion; SGA: small for gestational age.

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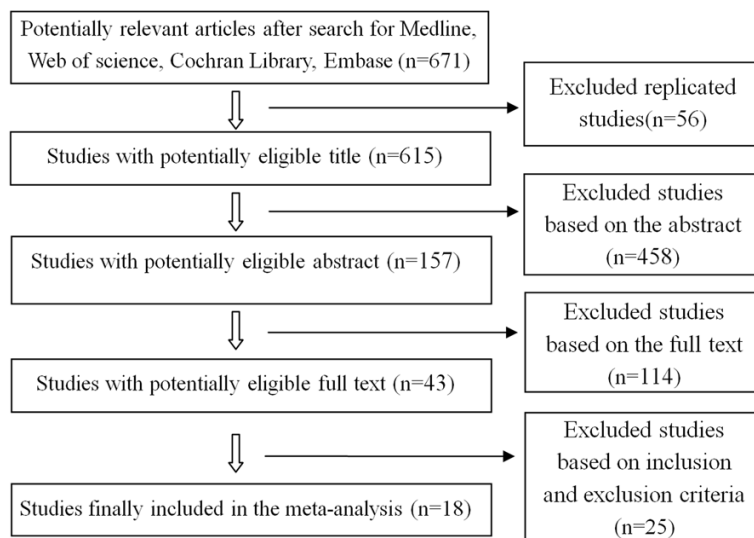


Figure 1. Flow diagram of selection of studies in the meta-analysis.

might result in DNA damage and do harm to embryo in its early phase of growth [8]. Tillett [9] reported an abnormality of mitochondrial DNA in oxidative stress caused by PM10. What's more, inhaling PM might induce placental inflammatory and subsequently result in impaired transplacental nutrient exchange. Alterations in blood coagulate ability, whole blood viscosity, endothelial function, hemodynamic response and so on, could represent other potential mechanisms of PM toxicity [10].

Even though a growing number of studies have been trying to explore associations between air pollution and adverse pregnancy outcomes, particularly low birth weight [11-15], preterm birth [16-21], birth defects [22-26], stillbirth [27-32], spontaneous abortion (SAB) [8, 33-45] and SGA [12, 14, 38-44]. The effects of exposure to PM on an increase in these pregnancy outcomes have not been consistently demonstrated in different population studies around the world. A meta-analysis has been published to show associations between maternal exposure to PM2.5 and the change of birth weight, LBW, PTB and SGA [46]. However, none of a review or meta-analysis has described the relationship between PM (both PM2.5 and PM10) and three adverse pregnancy outcomes of stillbirth, spontaneous abortion (SAB) and SGA. Therefore, the purpose of this meta-analysis was to estimate the effects of exposure to PM2.5 and PM10 by three trimesters and the entire pregnancy period on the occurrence of SAB, stillbirth and SGA, drawing coherent and consis-

tent conclusion and subsequently providing evidence for tackling the health effects of air pollution.

Materials and methods

Databases

We searched the Medline, EMBASE, Cochrane and Web of Science databases with the following keywords: "particulate matter", "stillbirth", "spontaneous abortion", "small for gestational age", "fetal growth retardation". The search strategy in the Medline database was as below: [MeSH] particulate matter and [MeSH] stillbirth; [MeSH] particulate matter and [MeSH] spontaneous abortion; ([MeSH] particulate matter and [MeSH] Fetal Growth Retardation) or ([MeSH] particulate matter and [MeSH] Small for Gestational Age). Similar literature retrieval processes were conducted in the other databases according to different requirements. Bibliographic references and lists of relevant review articles were manually searched. Only peer-reviewed original articles published in English were considered. We limited our search to articles published from start to 31 December 2015.

Selection of articles and extraction of data

Inclusion criteria: (1) singleton pregnancy with outcomes of SAB, stillbirth, SGA and normal delivery of livebirth; (2) had a history of maternal exposure to PM2.5 and PM10 during pregnancy; (3) original studies providing odds ratio (ORs) and 95% confidence intervals (CIs); (4) study designs were limited to cohort, case-control and cross sectional studies. Exclusion criteria: (1) did not meet inclusion criteria; (2) reviews, comments and lecture; (3) repeat literature; (4) the results in studies could not be transformed into odds ratio (ORs) and 95% confidence intervals (CIs); (5) animal studies; (6) only to explore the mechanism of stillbirth, SGA and SAB. Data were extracted by two independent investigators (Yifei Lu and Haiping Zhao) and conflicts were adjudicated by the third investigator (Dian He). The study design, study population, adjustment and potential confounders were summarized in **Table 1**.

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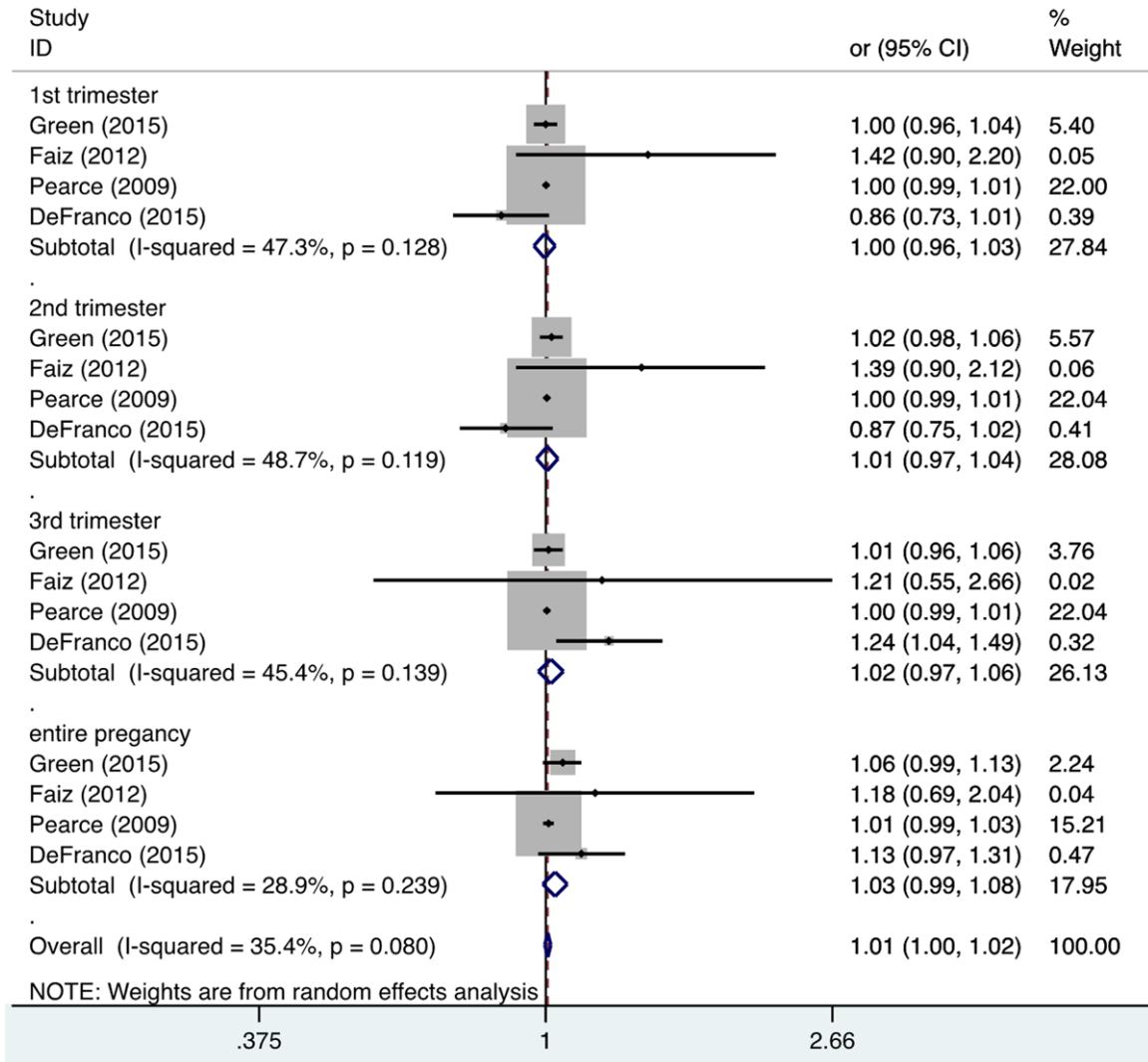


Figure 2. Forest plots of meta-analysis in the associations between different PM_{2.5} expose trimesters with stillbirth.

Statistical analysis

We used OR value as the overall effect indicator. ORs were pooled according to a standardized increment in pollutant concentration (10 µg/m³ for PM_{2.5} and PM₁₀). Most of the studies used generalized linear models, and therefore a linear relation between exposure and outcome was assumed. Standardized risk estimates were calculated for each study using the following formula [47]:

$$OR_{(standardised)} = OR_{(original)}^{\text{Increment}(10)/\text{Increment}(original)}$$

Some studies used multiple regressions to analyze the data and adjust for individual characteristics of the population, such as marital status, tobacco use, alcohol use, education, race, age, and others. Adjusted risk estimates were

pooled after controlling the meteorological, temporal and seasonal parameters in **Table 1**.

All of the statistical analyses were conducted in Stata version 12.0 (Stata Corp., TX, USA), and a *P* value <0.05 was considered statistically significant. Heterogeneity among studies was estimated using Chi-square test. A fixed-effects model would be selected if *P*>0.1 and *I*²<50%; otherwise, a random-effects model worked. Egger's test were used to assess publication bias. A sensitivity analysis was used to assess the stability of the results.

Results

In total, 671 articles were obtained from literature search. Among them, 628 articles were excluded for without eligible titles and abs-

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Table 2. Results of association, heterogeneity test and Egger's test between PM and pregnancy outcomes in different groups

PM and Outcomes	Trimester	No. of studies	Test of association		Test of heterogeneity		Egger's test
			OR	95% CI	I ² (%)	P value	P value
PM2.5 and stillbirth	Entire pregnancy	4	1.032	0.990 to 1.077	28.9	0.239	0.099
	First trimester	4	0.996	0.960 to 1.033	47.3	0.128	0.940
	Second trimester	4	1.005	0.969 to 1.043	48.7	0.119	0.901
	Third trimester	4	1.018	0.975 to 1.063	45.4	0.139	0.242
PM10 and stillbirth	Entire pregnancy	1	0.980	0.945 to 1.016	-	-	-
	First trimester	2	0.998	0.937 to 1.064	54.1	0.140	-
	Second trimester	2	1.005	0.905 to 1.116	81.1	0.021	-
	Third trimester	2	1.021	0.919 to 1.134	90.9	0.001	-
PM10 and SAB	First trimester	3	1.340	1.043 to 1.721	62.4	0.070	0.751
PM2.5 and SGA	Entire pregnancy	6	1.151	1.104 to 1.200	0	0.877	0.825
	First trimester	6	1.074	1.046 to 1.103	5	0.385	0.236
	Second trimester	5	1.058	1.019 to 1.100	58.1	0.049	0.755
	Third trimester	5	1.062	1.042 to 1.083	13.4	0.329	0.681

SAB: spontaneous abortion; SGA: small for gestational age. Test of heterogeneity was not conducted for one study. Egger's test was not conducted for two studies.

tracts. After reading the full texts of the remaining 43 articles, finally 18 studies met the inclusion criteria. Four studies explored the association between maternal exposure to PM2.5 and stillbirth [27-29, 31]. Nine studies investigated the effects of PM2.5 on SGA [12, 14, 38-44]. Two and three, respectively, examined the risk of PM10 on stillbirth and SAB [30, 32, 34-36]. The flow chart of selecting articles was shown in **Figure 1**. The details of these studies were given in **Table 1**.

PM2.5 and stillbirth

In this study, four articles examining the risk of PM2.5 on stillbirth based on the first trimester, second trimester, third trimester and the entire pregnancy period came into final analysis. Heterogeneity was observed for PM2.5 with stillbirth, and random-effects model was used to analyze the overall effect based on I² of different gestational exposure periods ranging from 28.9% to 48.7%. No significant associations were seen between stillbirth and maternal exposure to PM2.5 in the first (OR = 0.996, 95% CI = 0.960-1.033), second (OR = 1.005, 95% CI = 0.969-1.043), third (OR = 1.018, 95% CI = 0.975-1.063) trimesters and the entire pregnancy trimester (OR = 1.032, 95% CI = 0.990-1.077) (**Figure 2**). According to Egger's test, no publication bias were found in the

above four analyses for all the value of P>0.05 (**Table 2**). After sequentially excluding each study, statistically similar results were obtained, suggesting our results of meta-analysis were robust.

PM10 and stillbirth

Two studies explored the associations between PM10 of three trimesters' exposure and stillbirth. The Chi-square test implied the existence of heterogeneity. With the random-effects model, no statistically significant associations were observed between stillbirth and maternal exposure to PM2.5 in the first (OR = 0.998, 95% CI = 0.937-1.064), the second (OR = 1.005, 95% CI = 0.905-1.116) and the third (OR = 1.021, 95% CI = 0.919-1.134) trimesters. In additional, with regard to the entire pregnancy, only one literature mentioned a lack of association between them (OR = 0.980, 95% CI = 0.945-1.016) (**Figure 3**).

PM2.5 and small for gestational age

In this study, six, five, five, six articles, respectively, were reviewed to assess the effects of PM2.5 on SGA during the first, second and third trimesters as well as the entire pregnancy period. Heterogeneity was observed for PM2.5 and SGA with I² up to 58.1%, and the random-effects model was applied to analyze the over-

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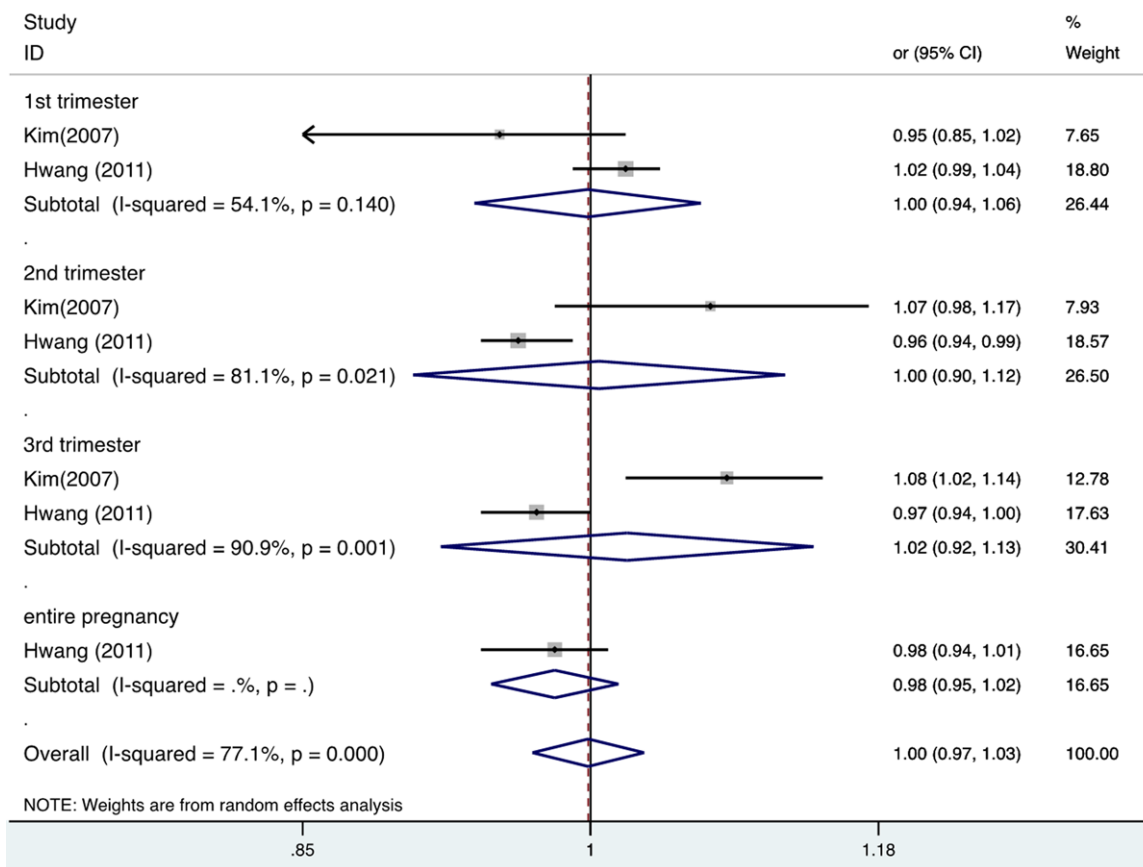


Figure 3. Forest plots of meta-analysis in the associations between different PM10 expose trimesters with stillbirth.

all effect. The positive associations were identified between SGA and maternal exposure to PM2.5 in the first (OR = 1.074, 95% CI = 1.046-1.103), the second (OR = 1.058, 95% CI = 1.019-1.100), the third (OR = 1.062, 95% CI = 1.042-1.083) trimesters and the entire pregnancy period (OR = 1.151, 95% CI = 1.104-1.200), which indicated that with every 10 $\mu\text{g}/\text{m}^3$ increase in PM2.5, the risk of SGA would increase 7.4%, 5.8%, 6.2% and 15.1%, respectively (Figure 4). With all the value of $P > 0.05$ in Egger's test, no publication bias was found in all analysis (Table 2). A sensitivity analysis was used to assess the stability of the results. After removing each article sequentially, statistically steady results were obtained, suggesting our results of meta-analysis were robust. However, none article revealed the relationship between PM10 and SGA, and that was why we did not perform meta-analysis between them.

PM10 and spontaneous abortion

We found three literatures evaluating the relationship between PM10 and SAB. Heterogeneity

was observed ($I^2 = 62.4\%$) and the random-effects model was used. The pooled outcome of these three studies on the first gestational trimester was significantly positive with a 10 $\mu\text{g}/\text{m}^3$ increase in PM10 (OR = 1.340, 95% CI = 1.043-1.721), indicating an 34% increased risk of SAB (Figure 5). Egger's test showed that publication bias was not seen in this analysis. In addition, sensitivity analysis indicated that our pooled result was robust. No article revealing the risk of PM2.5 on SAB was found.

Discussion

In this study, 18 articles were selected into final analysis to show the associations between maternal exposure to PM at different gestational periods and adverse pregnancy outcomes. In this study, the positive associations between PM2.5 and SGA were found on the first term, the second term, the third term and the entire pregnancy exposure, which indicated that with every 10 $\mu\text{g}/\text{m}^3$ increase in PM2.5, the risk of SGA would increase 7.4%, 5.8%, 6.2% and 15.1%, respectively. Besides, the association

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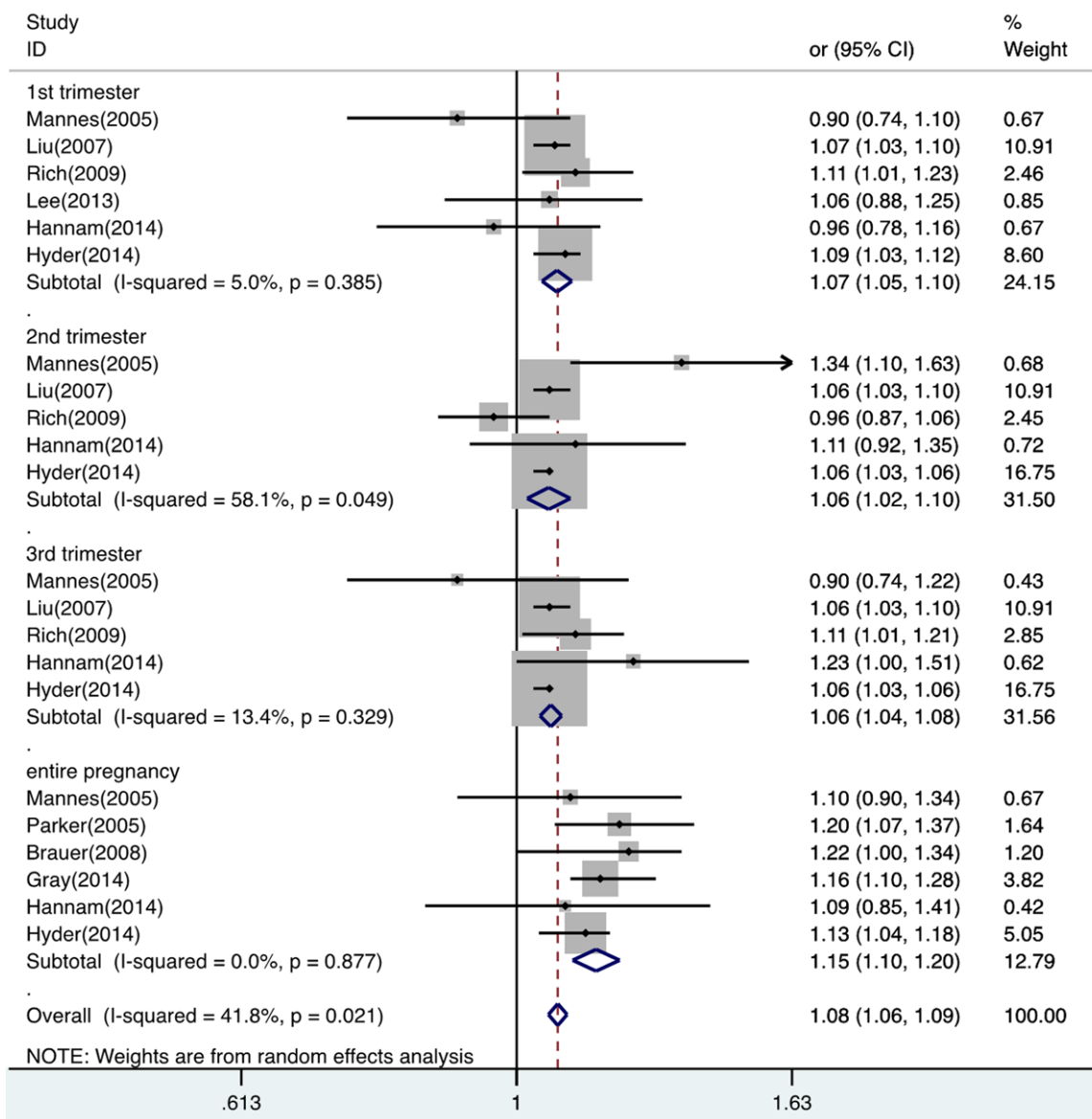


Figure 4. Forest plots of meta-analysis in the associations between different PM expose trimesters with small for gestational age.

between PM₁₀ exposure levels in early pregnancy period and SAB was statistically significant, revealing that for every 10 µg/m³ increase in PM_{2.5}, the risk of SAB would increase by 34%. However, no significant association was found between PM and stillbirth.

This study didn't reveal that increases in stillbirth were associated with higher levels of ambient PM. The study by Hwang [32] suggested a positive association between exposure to SO₂ during pregnancy and stillbirth. Likewise, Faiz [10] stated that deliveries exposed to high

levels of SO₂ and CO were more likely to give stillbirth. However, the association between stillbirth and ambient PM was unclear, for the results of different studies were inconsistent. A study performed in Seoul, Korea [30] demonstrated that per 10-µg/m³ increase in PM₁₀ was positively associated with a 8% increase in risk of stillbirth (OR = 1.08, 95% CI = 1.02-1.14). Moreover, DeFranco [31] found that the risk of stillbirth was increased with exposure to high PM_{2.5} levels in the third trimester of pregnancy (OR = 1.42, 95% CI = 1.06-1.91). On the contrary, some other researches [27-29] did

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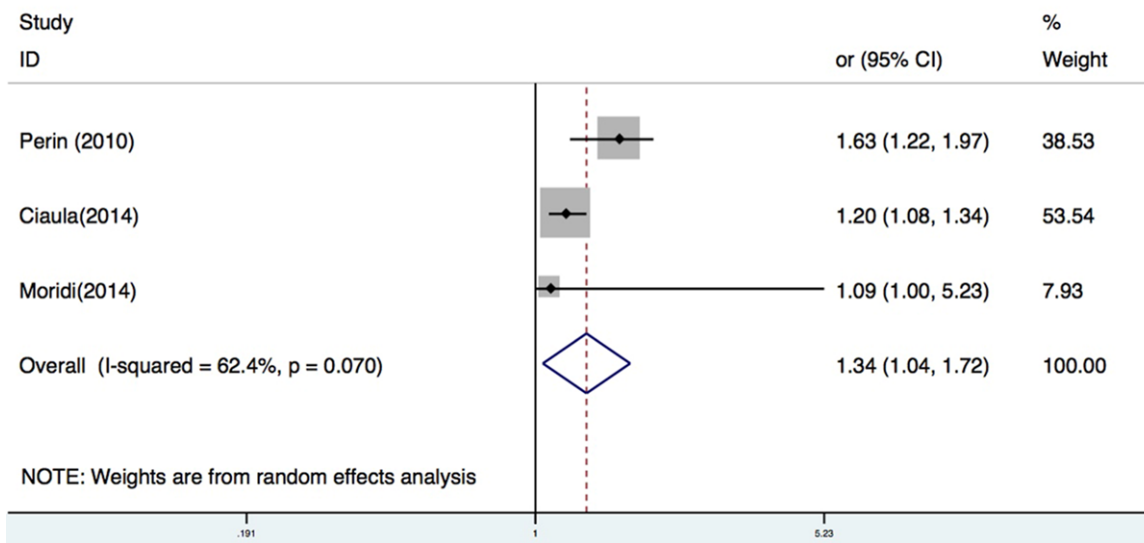


Figure 5. Forest plots of meta-analysis the associations between PM10 with spontaneous abortion.

not find such a positive association. Until nowadays, the biologic mechanism by which ambient PM may affect stillbirth remains unclear. Many factors, such as ethnic differences, economic status, outdoor activities, could have an impact on the research. Therefore, more studies are needed in the future to investigate the possible relationship between ambient PM and stillbirth.

This meta-analysis indicated a deleterious effect of PM_{2.5} exposure on SGA in three trimesters and the entire of pregnancy. There was a significant sense identifying fetuses suffered from SGA, since their perinatal mortality rates were six times more than their normal growing peers. Even worse, the risk of poor developmental results could persist into later childhood and then extend into adolescence [48]. Recent years, some studies have linked PM with SGA. Dejmek [49] reported the impact of PM_{2.5} exposure on negative fetal growth effects, including SGA, based on the population settled in a polluted area of the Northern Bohemian region of the Czech Republic. Hertel [50] claimed that a 3.91 µg/m³ exposure increase in PM_{2.5} would lead to an increase in high sensitivity C-reactive protein (CRP) and fibrinogen level. And elevated inflammatory status in pregnant women was correlated with poor developmental outcomes [51]. The combined estimate of our study was consistent with most original studies.

In this study, we found that PM₁₀ and SAB were highly associated. The association between ambient air pollution and SAB was well documented in many researches [52-55]. Enkhmaa [33] showed us a strongly significant correlation coefficient of PM₁₀ ($r > 0.9$) in a dose-response toxicity curve, revealing a strong connection between PM₁₀ and SAB. The mechanism of how PM₁₀ had effect on SAB might be explained as genetic damage, for chromosomal abnormalities have been frequently described in early SAB [56], especially in industrial areas. Furthermore, exposure to PM might alter markers of placental growth and function, then finally cause poor pregnancy outcomes [57]. All of the above evidence could support our conclusion in this study.

Several limitations of this study should be considered. First, we found different degrees of heterogeneity across PM, which could be partly explained by differences in population demography, sample size, exposure assessment, compounds of particulate matters, etc. Secondly, we only described the impact of single pollutants without taking combined effects of multi-pollutants into account. Third, in this study, the term of intrauterine growth retardation (IUGR) was treated as the same as SGA, for most articles defined them in the same way. Finally, a limited number of literatures were included in our final analysis, for a relatively small number of researches focused on the adverse pregnan-

cy outcomes of stillbirth, SAB and SGA when compared with which of preterm, low birth weight and birth defects. Thus, more researches on such subjects are still needed.

Acknowledgements

This study was supported by: The Natural Science Foundation of China (NSFS) [no. 81402689]. None pharmaceutical company or other agency was involved in this study, and we had full access to all the data and had final responsibility for the decision to submit for publication.

Disclosure of conflict of interest

None.

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