View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Environmental Pollution 211 (2016) 38–47

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

The associations between birth weight and exposure to fine particulate matter ($PM_{2.5}$) and its chemical constituents during pregnancy: A meta-analysis

Xiaoli Sun [a], Xiping Luo [a, **], Chunmei Zhao [a], Bo Zhang [b], Jun Tao [c], Zuyao Yang [d], Wenjun Ma [e], Tao Liu [e, *]

[a] Gynecology Department, Guangdong Women and Children Hospital, Guangzhou, 511442, China
[b] Department of Preventive Medicine, School of Public Health, Sun Yat-sen University, Guangzhou, 510080, China
[c] South China Institute of Environmental Sciences, Ministry of Environmental Protection, Guangzhou, 510085, China
[d] Division of Epidemiology, The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, 999000, China
[e] Guangdong Provincial Institute of Public Health, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, 511430, China

ARTICLE INFO

Article history:
Received 16 August 2015
Received in revised form
14 December 2015
Accepted 14 December 2015
Available online 29 December 2015

Handling Editor: Elena Paoletti.

Keywords:
Air pollution
Fine particulate matter
Chemical constitute
Birth weight
Meta-analysis

ABSTRACT

We performed this meta-analysis to estimate the associations of maternal exposure to $PM_{2.5}$ and its chemical constituents with birth weight and to explore the sources of heterogeneity in regard to the findings of these associations. A total of 32 studies were identified by searching the MEDLINE, PUBMED, Embase, China Biological Medicine and Wanfang electronic databases before April 2015. We estimated the statistically significant associations of reduced birth weight ($\beta = -15.9$ g, 95% CI: −26.8, −5.0) and LBW (OR = 1.090, 95% CI: 1.032, 1.150) with $PM_{2.5}$ exposure (per 10 $\mu g/m^3$ increment) during the entire pregnancy. Trimester-specific analyses showed negative associations between birth weight and $PM_{2.5}$ exposure during the second ($\beta = -12.6$ g) and third ($\beta = -10.0$ g) trimesters. Other subgroup analyses indicated significantly different pooled-effect estimates of $PM_{2.5}$ exposure on birth weight in studies with different exposure assessment methods, study designs and study settings. We further observed large differences in the pooled effect estimates of the $PM_{2.5}$ chemical constituents for birth weight decrease and LBW. We concluded that $PM_{2.5}$ exposure during pregnancy was associated with lower birth weight, and late pregnancy might be the critical window. Some specific $PM_{2.5}$ constituents may have larger toxic effects on fetal weight. Exposure assessment methods, study designs and study settings might be important sources of the heterogeneity among the included studies.

© 2015 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Ambient particulate matter, especially fine particulate matter ($PM_{2.5}$, aerodynamic diameter <2.5 μm), has been linked to a number of adverse health endpoints, including morbidity and mortality due to cardiovascular and respiratory diseases (Hoek et al., 2013). It has been demonstrated that inhaled $PM_{2.5}$ can penetrate the gas exchange region of the lungs, enter the blood-stream, and cause systemic toxicity in humans (Parker and Woodruff, 2008).

Birth weight is an important indicator of fetal growth, and low birth weight (LBW) is associated with perinatal morbidity and mortality as well as health issues during adolescence and beyond. These effects include asthma, a low intelligence quotient (IQ) and hypertension (Harris et al., 2014). Therefore, understanding the risk factors for LBW with the goal of reducing the incidence of LBW is profoundly significant to public health. In the last decade, a growing number of studies have estimated the association of $PM_{2.5}$

Abbreviations: $PM_{2.5}$, fine particulate matter with aerodynamic diameter <2.5 μm; OR, odds ratio; CI, confidence interval; USA, The United States of America; LBW, low birth weight; PLBW, preterm low birth weight; IQ, intelligence quotient; NA, Data not available; Al, aluminum; K, potassium; Zn, zinc; Ni, nickel; Ti, titanium; V, vanadium; OC, organic carbon; NO_3^-, nitrate; SO_4^{2-}, sulfate; EC, elemental carbon; Si, silicon; S, sulfur; Cl, chlorine; Pb, lead; Ca, calcium; NH_4^+, ammonium ion; Na^+, sodium ion.

* Corresponding author. No. 160, Qunxian Road, Panyu District, Guangzhou, 511430, China.
** Corresponding author. No. 521, Xingnan Road, Panyu District, Guangzhou, 511442, China.
E-mail addresses: luoxiping07@aliyun.com (X. Luo), gztt_2002@163.com (T. Liu).

http://dx.doi.org/10.1016/j.envpol.2015.12.022
0269-7491/© 2015 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

exposure during pregnancy with birth weight and LBW. While some studies observed significant associations between $PM_{2.5}$ exposure and lower birth weight (Basu et al., 2004; Bell et al., 2007, 2008; Gray et al., 2014; Harris et al., 2014; Hyder et al., 2014; Parker et al., 2005; Savitz et al., 2014), but other studies did not find such associations (Brauer et al., 2008; Gehring et al., 2011; Madsen et al., 2010; Parker and Woodruff, 2008). These inconsistent and controversial results indicate the need to quantitatively synthesize and interpret the available evidence to provide more explicit information for policy decisions and clinical use.

Meta-analysis is the most commonly used statistical technique to quantitatively synthesize results from two or more separate studies (Higgins and Green, 2008). To our knowledge, four meta-analyses have been conducted to quantitatively summarize the association between maternal $PM_{2.5}$ exposure during pregnancy and birth weight (Dadvand et al., 2013; Sapkota et al., 2012; Stieb et al., 2012; Zhu et al., 2014). However, substantial heterogeneity among the included studies was observed in all four meta-analyses (Dadvand et al., 2013; Sapkota et al., 2012; Stieb et al., 2012; Zhu et al., 2014). According to the Cochrane Handbook for Systematic Reviews, it is not appropriate to simply combine the results of different studies and present only a single summary estimate of the association when there is substantial between-study heterogeneity. Instead, emphasis should be placed on an exploration of the source of heterogeneity. Unfortunately, the efforts of some previous meta-analyses to explore the source of heterogeneity were limited by the small number of studies included for analysis (Sapkota et al., 2012; Stieb et al., 2012). In the past several years, a number of new studies have been conducted to estimate the association of maternal $PM_{2.5}$ exposure with birth weight. These studies provide an opportunity to quantitatively explore the sources of heterogeneity among the previous studies and meta-analyses.

In addition, it is well known that the toxic effect of $PM_{2.5}$ largely depends on its chemical constituents. The lack of scientific evidence regarding which $PM_{2.5}$ chemical constituents have higher toxicity is one of the greatest research gaps (Pope III and Dockery, 2006). In the past several years, some studies have attempted to determine which chemical constituents of $PM_{2.5}$ are primarily responsible for reducing neonatal birth weight, but the results have been inconsistent and controversial (Basu et al., 2014; Bell et al., 2012, 2010; Darrow et al., 2011; Ebisu and Bell, 2012; Laurent et al., 2014; Wilhelm et al., 2012). Therefore, it was necessary to conduct a meta-analysis to quantitatively synthesize the results from the various studies.

In this analysis, we systemically collected previously published studies that estimated the effects of $PM_{2.5}$ exposure during pregnancy on birth weight and/or LBW and then employed a meta-analysis model to quantitatively evaluate the effects of exposure to $PM_{2.5}$ and its major chemical constituents during different pregnancy phases on birth weight and LBW. We further explored the impacts of the exposure measurement methods, study settings and study designs on the meta-estimates of the effects of $PM_{2.5}$.

2. Materials and methods

We searched the MEDLINE, PUBMED and EMBASE databases as well as China Biological Medicine and Wanfang databases during January and March in 2015 for all studies published before March 2015. Our search strategy used a combination of the following key words: “air pollution”, “particulate matter”, “fine particulate matter”, “fine particles”, “PM”, “$PM_{2.5}$”, “PM $_{2.5}$”, “component”, “constituent”, “composition”, “birth weight”, “change in birth weight”, “low birth weight”, “LBW”, “adverse birth outcomes” and “adverse pregnancy outcomes”. We also manually searched the references of every primary study for additional publications. Further publications were also identified by examining review articles. Only publications in English or Chinese were included.

2.1. Study selection

2.1.1. Inclusion and exclusion criteria

We initially screened all of the study titles and abstracts. Studies were excluded if they did not address the relationship between $PM_{2.5}$ and birth weight. The remaining studies were marked as potentially eligible and were further evaluated by two independent authors. A study was included in this meta-analysis if it met the following criteria: (a) the study included $PM_{2.5}$ exposure during pregnancy, and the pregnancy outcomes measured birth weight and/or LBW; birth weight was measured as a continuous variable; and LBW was defined as a live birth weighing less than 2500 g, including term LBW (TLBW) and preterm LBW (PLBW); (b) the study provided the sample size, partial regression coefficient (β) for birth weight, odds ratio (OR) for LBW as well as its 95% confidence intervals (CI), or information that could be used to infer these results; and (c) if more than one study was identified for the same population, only the study that included the most recent population or the most information was selected. Accordingly, studies that did not meet the above criteria were excluded. The study selection process is presented in detail in Fig. 1.

2.1.2. Data extraction

The following information was extracted from each study: authors; year and source of publication; study period; study setting; study design; $PM_{2.5}$ exposure measurement methods; data sources; sample size; $PM_{2.5}$ exposure windows; exposure mean and range; β and/or OR; and their 95% CIs. If a study provided associations of $PM_{2.5}$ exposure during the entire pregnancy and trimester-specific periods with birth weight, all of the estimates were extracted.

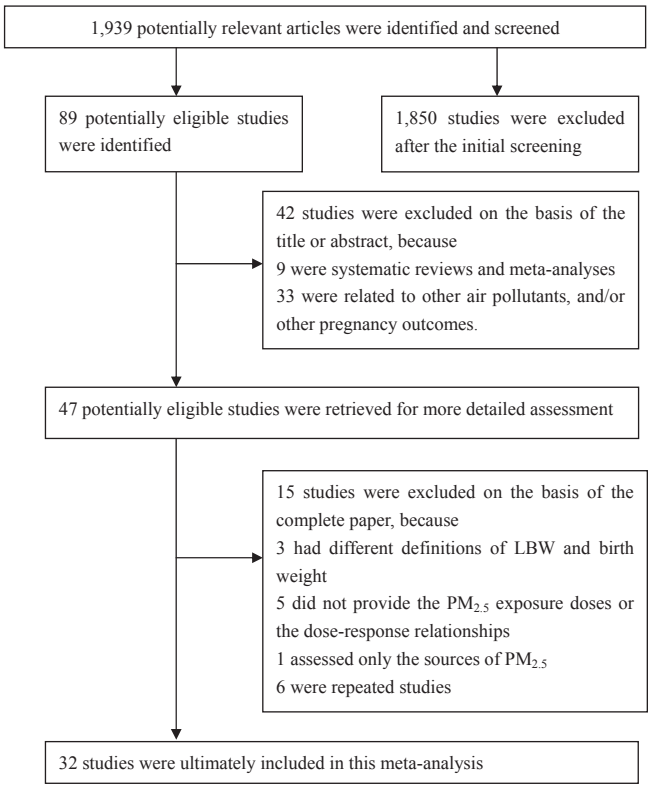

Fig. 1. Flow chart for the study selection process.

Several studies assessed $PM_{2.5}$ exposure based on both monitoring network data and remote sensing data; we preferentially chose estimates based on the monitoring network because this assessment method was more common across all studies, which could potentially reduce the heterogeneity between studies in this meta-analysis. In addition, we extracted estimates from single pollutant models only if they were fully adjusted for other covariates, because there is considerable co-linearity among pollutants originating from the same sources, and not all studies were adjusted for the same air pollutants other than $PM_{2.5}$. Eligibility assessments and all data extractions were carried out by two authors using a standard form, and discrepancies were resolved by discussion between the authors.

2.2. Meta-analysis and statistical analysis

Prior to performing the meta-analysis, we converted all risk estimates (β and OR) of $PM_{2.5}$ mass and its chemical constituents to a common exposure unit increase, which allowed us to pool estimates from different studies. We set a common exposure unit of effect as a 10 $\mu g/m^3$ increase in the $PM_{2.5}$ mass concentration. As for the $PM_{2.5}$ chemical constituents, we set two common exposure units (1 $\mu g/m^3$ and 10 ng/m^3) because the estimates for various constituents varied greatly. We combined the effect estimates for $PM_{2.5}$ constituents, such as Al, K and Zn using a 10 ng/m^3 unit, and for constituents such as OC, NO_3^- and EC, we used a 1 $\mu g/m^3$ increase.

We then conducted several meta-analyses of the identified studies to quantitatively estimate the associations of $PM_{2.5}$ exposure during the entire pregnancy and trimester-specific periods with birth weight. Several secondary analyses were also conducted to estimate the pooled effects of $PM_{2.5}$ exposure during the entire pregnancy on birth weight in subgroups that used different exposure measurement methods, study designs and study settings. These subgroup analyses aimed to explore the impact of these characteristics on the estimates of the effects of $PM_{2.5}$ exposure on birth weight and further test their impact on the heterogeneity among the reported associations. Three exposure measurement methods were identified in these included studies: individual level, semi-individual level, and regional level exposure assessments. Individual level exposure was assessed using complex dispersion models that included various databases including traffic, meteorology, roadway geometry, vehicle emission, air quality monitoring data, and land use (Berrocal et al., 2011; Darrow et al., 2011; Jedrychowski et al., 2009; Savitz et al., 2014). These models could estimate each subject's daily $PM_{2.5}$ exposure level with high accuracy. Semi-individual exposure was estimated using the daily $PM_{2.5}$ concentration from the monitoring station nearest to the individual's residence (Basu et al., 2014; Brauer et al., 2008). Regional level exposure was calculated using the average $PM_{2.5}$ concentration in a region or a grid with a low resolution. This method did not consider the variation in the $PM_{2.5}$ concentration within a region and assumed that all of the subjects in this region were exposed to the same $PM_{2.5}$ concentration (Bell et al., 2010; Ebisu and Bell, 2012). The study designs for all of the included studies were divided into two categories: retrospective and prospective. Several meta-regression analyses were also employed to explore the modification effects of study periods, exposure measurement methods, study designs and study settings on the associations between $PM_{2.5}$ exposure and birth weight.

To explore the possible heterogeneity of the study results, we hypothesized that the effect size might differ according to the methodological quality of the studies. The heterogeneity of the included studies was assessed using the Q statistic and I^2 statistic. Cochran's Q statistic was calculated by summing the squares of the deviations of the estimates from each study from the overall meta-analysis estimate by weighting each study's contribution. A P-value was obtained by comparing the Q statistic with a chi-square distribution with k-1 degrees of freedom, where k was the number of included studies (Higgins et al., 2003). If the P-value was <0.05, then a random-effects model was selected, otherwise a fixed-effects model was selected. The I^2 statistic [$I^2 = (Q-df)/Q \times 100$] describes the percentage of variation across studies that is due to heterogeneity rather than chance. A value of I^2>50% demonstrated that there is a statistically significant heterogeneity (Higgins et al., 2003). We also employed funnel plot asymmetry to detect the potential publication bias. An Egger's regression was applied to test the funnel plot symmetry, in which the inverse of the standard error was the independent variable and the standardized estimate of the effect size was the dependent variable (Egger et al., 1997).

Finally, a series of sensitivity analyses was performed to test the robustness of our results. Because some subgroup analyses included very few studies, we only conducted sensitivity analyses for the meta-analyses that included more than three studies. For each sensitivity analysis, we individually removed the single studies with the largest and the smallest estimates from the meta-analyses.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. We used R software (version 2.15.2; R Development Core Team 2012, www.R-project.org) to analyze the data, and the package "matafor" was used.

3. Results

3.1. Search results and study characteristics

A total of 89 studies were selected as potentially eligible publications. After excluding 42 studies (9 were reviews, and 33 did not assess $PM_{2.5}$ and/or birth weight), 47 studies were identified for a more detailed assessment. Fifteen studies were further excluded due to different definitions of LBW and birth weight (n = 3), not providing the $PM_{2.5}$ exposure doses or the dose–response relationship between $PM_{2.5}$ exposure and birth weight (n = 5), or assessing only the sources of $PM_{2.5}$ (n = 1) and repeated studies (n = 6). Finally, 32 studies were included in this meta-analysis, containing more than fifteen million subjects, of which 10 studies assessed birth weight, 12 studies assessed LBW, and 10 studies assessed both birth weight and LBW (Basu et al., 2014, 2004; Bell et al., 2012, 2010, 2007; Brauer et al., 2008; Brown et al., 2015; Dadvand et al., 2014; Darrow et al., 2011; Ebisu and Bell, 2012; Fleischer et al., 2014; Geer et al., 2012; Gehring et al., 2011; Gray et al., 2014; Ha et al., 2014; Hannam et al., 2014; Harris et al., 2014; Hyder et al., 2014; Jedrychowski et al., 2009; Kloog et al., 2012; Kumar, 2012; Laurent et al., 2014; Madsen et al., 2010; Mannes et al., 2005; Morello-Frosch et al., 2010; Parker and Woodruff, 2008; Parker et al., 2005; Pedersen et al., 2013; Savitz et al., 2014; Trasande et al., 2013; Vinikoor-Imler et al., 2014; Wilhelm et al., 2012). More than 300,000 LBW cases were included in the 22 studies that assessed the association between $PM_{2.5}$ and LBW. In particular, seven studies estimated the associations of the chemical constituents of $PM_{2.5}$ with birth weight and/or LBW (Basu et al., 2014; Bell et al., 2012, 2010; Darrow et al., 2011; Ebisu and Bell, 2012; Laurent et al., 2014; Wilhelm et al., 2012). Most of the included studies (23/32) were conducted in the USA. Detailed information for all of the included studies is shown in Table 1Table l.

3.2. Pooled estimate of the effect of the $PM_{2.5}$ mass concentrations on birth weight

We estimated a statistically significant decrease in birth weight

Table 1
Characteristics of the studies included in the meta-analysis.

Author	Location	Study duration	Exposure measurement method	Data source	No. of participants	No. of cases	Type of cases	Exposure window	OR/β (95%CI)	Exposure range (mean (IQR) μg/m^3)	$PM_{2.5}$ chemical constituents
Basu et al., 2004†	California, USA	2000	Semi-individual level and regional level	Monitoring network data	16,693	–		WP	β = −2.0 g (−3.4, −0.6)	18.5 (7.6)	
Basu et al., 2014*†	California, USA	2000 –2006	Semi-individual level	Monitoring network data	646,296	15,511	TLBW	WP	β = −7.0 g (−9.0, −4.0) OR = 1.01(0.98, 1.05)	18.7 (7.6)	Al, NH_4^+, Ca, Cl, EC, Pb, Ni, OC, K, Si, Na^+, SO_4^{2-}, S, Ti, NO_3^-, V, Zn
Bell et al., 2007†	Massachusetts and Connecticut, USA	1999 –2002	Regional level	Monitoring network data	358,504	14,376	TLBW and PLBW	WP	β = −14.7 g (−17.1, −12.3) OR = 1.05 (1.02, 1.09)	11.9 (2.2)	
Bell et al., 2010*†	Massachusetts, and Connecticut, USA	2000 –2004	Regional level	Monitoring network data	76,788	1671	TLBW	WP and TS	β = −3.0 g (−9.0, 2.0) OR = 1.07 (0.99, 1.17)	14.0 (3.6)	Zn, EC, Si, Al, V, Ni, Cl, S,
Bell et al., 2012*†	Massachusetts, and Connecticut, USA	2000 –2004	Regional level	Monitoring network data	76,788	1671	TLBW	WP	※	14.0 (3.6)	K, Ti
Brauer et al., 2008‡	Vancouver, Canada	1999 –2002	Semi-individual level	Monitoring network data	70,249	894	TLBW	WP	OR = 0.98 (0.92 –1.05)	5.1 (1.1)	
Brown et al., 2015†	New York, USA	2001 –2006	Semi-individual level	Monitoring network data	480,430	9782	TLBW	WP and TS	OR = 0.97(0.91 –1.04)	11.0 (2.4)	
Dadvand et al., 2014‡	Barcelona, Spain	2001 –2005	Individual level	Monitoring network data, emission, and land use data	6438	190	TLBW	WP and TS	OR = 1.17 (0.98, 1.39)	16.9 (3.1)	
Darrow et al., 2011*†	Atlanta, USA	1994 –2004	Regional level and individual level	Monitoring network data	406,627	–		TS	※	16.5 (5.0)	SO_4^{2-}, NO_3^- EC, OC
Ebisu and Bell, 2012*†	Northeastern, mid-Atlantic, USA	2000 –2007	Regional level	Monitoring network data	1,207,800	34,038	TLBW	WP	OR = 1.03 (0.99, 1.07)	13.4 (2.7)	Zn, EC, Si, Al, V, Ni, Cl, Ti, NH_4^+, Ca, Pb, OC, Na^+, SO_4^{2-}, NO_3^-
Fleischer et al., 2014†	22 countries	2004 –2008	Regional level	Remote sensing data	192,900	16,467	TLBW and PLBW	WP	OR = 1.15 (1.01,1.32)	1.4–98.1 (NA)	
Geer et al., 2012†	Texas, USA	1998 –2004	Regional level	Monitoring network data	759,465	–		WP	β = 2.5 g (0.6, 4.4)	12.6 (1.0)	
Gehring et al., 2011‡	North, west, and center of the Netherlands	1996 –1997	Individual level	Monitoring network data and land use regression model	3408	–		WP and TS	β = 3.0 g (−20.3, 26.3)	20.1 (4.6)	
Gray et al., 2014†	North Carolina, USA	2002 –2006	Regional level	Monitoring network data	457,642	30,458	TLBW and PLBW	WP	β = −3.1 g (−3.3, −2.9) OR = 1.02 (0.99, 1.04)	13.6 (2.0)	
Ha et al., 2014†	Florida, USA	2004 –2005	Regional level and semi-individual level	Monitoring network data	123,207	2887	TLBW	WP and TS	OR = 1.05(0.99,1.11)	9.9 (2.0)	
Hannam et al., 2014†	Northwest England	2004 –2008	Semi-individual level and individual level	Monitoring network data	265,613	–		WP and TS	β = 5.0 g (−11.0, 22.0)	22.1 (4.6)	
Harris et al., 2014†	7 states in USA	2001 –2004	Regional level	Monitoring network data	1,374,875	34,785	TLBW	WP and TS	OR = 1.03 (1.02, 1.04)	11.9 (NA)	
Hyder et al., 2014†	Connecticut and Massachusetts, USA	2000 –2006	Semi-individual level	Monitoring network	619,675	11,641	TLBW	WP and TS	β = −6.2 g (−7.9, −4.6) OR = 1.01 (0.98, 1.04)	11.9 (2.4)	
Jedrychowski et al., 2009‡	Krakow, Poland	2001 –2004	Individual level	Personal monitor	481	–		TS	β = 97.2 (201, 6.6)g	43.8 (29.3)	
Kloog et al., 2012†	Massachusetts, USA	2000 –2008		Remote sensing data	634,244	–		WP and TS	β = −13.8 g (−21.1, −6.1)	9.6 (5.3)	

(*continued on next page*)

Table 1 (*continued*)

Author	Location	Study duration	Exposure measurement method	Data source	No. of participants	No. of cases	Type of cases	Exposure window	OR/β (95%CI)	Exposure range (mean (IQR) μg/m^3)	$PM_{2.5}$ chemical constituents
			Semi-individual level								
Kumar, 2012†	Chicago, USA	2000–2004	Semi-individual level	Monitoring network data	82,694	5789	TLBW	WP and TS	β = −1.1 g (−1.9, −0.3) OR = 1.001(0.991, 1.011)	17.9 (−)	
Laurent et al., 2014*†	California, USA	2001–2008	Semi-individual level	Monitoring network data	960,945	44,973	TLBW	WP	OR = 1.02 (1.01,1.03)	17.4 (5.8)	EC, Ni, K, Ti, Pb, OC
Madsen et al., 2010†	Oslo, Norway	1999–2002	Semi-individual level	Monitoring network data	25, 229	303	TLBW	WP	β = 4.5 g (−10.9, 19.9) OR = 0.9 (0.6,1.2)	12.6 (1.4)	
Mannes et al., 2005†	Sydney, Australia	1998–2000	Regional level	Monitoring network data	138, 056	–		TS	β = 0.36 g (−2.29,3.01)	9.4 (4.7)	
Morello-Frosch et al., 2010†	California, USA	1996–2006	Semi-individual level	Monitoring network data	3,545,177	81,539	TLBW	WP and TS	β = −11.4 g (−13.5, −9.3) OR = 1.00 (0.98, 1.01)	16.7 (9.0)	
Parker et al., 2005†	California, USA	1999–2000	Semi-individual level	Monitoring network data	18,247	–		WP and TS	β = −35.3 g (−58.6, −12.0)	15.4 (6.5)	
Parker and Woodruff, 2008†	Throughout the USA	2001–2003	Regional level	Monitoring network data	44,334	568	TLBW	WP	β = 4.6 g (−6.1, 15.3) OR = 1.00 (0.91, 1.10)	9.8–19.9 (NA)	
Pedersen et al., 2013‡	12 European countries	1994–2011	Individual level	Monitoring network data, emission, and land use data	50,151	675	TLBW	WP	β = −7.0 g (−17.0, 2.0) OR = 1·18 (1·06, 1·33)	16.5 (−)	
Savitz et al., 2014†	New York, USA	2008–2010	Individual level	Monitoring network data, emission, and land use data	252,967	–		WP and TS	β = −48.4 g (−62.3, −34.5)	10.4 (2.5)	
Trasande et al., 2013†	Throughout the USA	2000–2006	Regional level	Monitoring network data	2,675,679	67,545	TLBW	TS	OR = 1.12 (1.07, 1.16)	12.6(6.0)	
Vinikoor-Imler et al., 2014†	North Carolina, USA	2003–2005	Semi-individual level	Monitoring network data	297,043	6398	TLBW	TS	OR = 1.01(0.97,1.06)	14.0 (3.5)	
Wilhelm et al., 2012*†	California, USA	1999–2000	Semi-individual level	Monitoring network data	82,395	1866	TLBW	WP	OR = 1.01 (0.95, 1.07)	17.9 (2.4)	V

-: The number of cases was not available because these studies only assessed the association between $PM_{2.5}$ exposure and birth weight. NA: Data not available; WP: Whole pregnancy; TS: Trimester specific; TLBW: term low birth weight; PLBW: preterm low birth weight. *: Studies that assessed the associations of $PM_{2.5}$ chemical constitutes with birth weight and/or LBW. †: Retrospective studies. ‡:Prospective studies. ※: The estimates of OR/β were not available because these studies only investigated the effects of $PM_{2.5}$ chemical constituents.

(β = −15.9 g, 95% CI: −26.8, −5.0) associated with exposure to a 10 μg/m^3 increment in the $PM_{2.5}$ mass concentration during the entire pregnancy across 17 studies with a significant between-study heterogeneity (Q = 185.38, P < 0.001) (Table 2 and Fig. 2). The pooled estimate of the effect of $PM_{2.5}$ exposure during the first trimester on birth weight was not statistically significant (β = −8.3 g, 95% CI: −17.0, 0.4), but the pooled effects during the second trimester (β = −12.6 g, 95% CI: −21.7, −3.1) and third trimester (β = −10.0 g, 95% CI: −16.6, −3.5) were statistically significant (Table 2).

To explore the sources of between-study heterogeneity, a series of subgroup analyses were conducted. The results indicated large differences in the effect estimates for $PM_{2.5}$ exposure in studies with different exposure assessment methods, study designs, and study settings. Significant pooled estimates of the effects of $PM_{2.5}$ exposure were found in studies that employed a semi-individual exposure method (β = −15.2 g, 95% CI: −20.7, −9.7), in retrospective studies (β = −16.7 g, 95% CI: −28.7, −4.8) and studies from the USA (β = −18.8 g, 95% CI: -31.4, −6.3). In particular, only two prospective studies were included in the meta-analysis. The decreases in birth weight for each 10 μg/m^3 increment in $PM_{2.5}$ concentration during the entire pregnancy were −14.0 g (95% CI: -32.0, 4.0) and 6.5 g (95% CI: −44.1, 57.2), and their pooled estimate was −11.7 g (95% CI: −28.7, 5.3) (Table 2). The results of meta-regression analysis showed similar modification effect patterns of the study characteristics, but none of the tests was statistically significant (Appendix Fig. A.1).

3.3. Pooled estimate of $PM_{2.5}$ mass concentrations on LBW

There was a statistically significant increase (OR = 1.090, 95% CI: 1.032, 1.150) in the LBW risk in association with each 10 μg/m^3 increment in $PM_{2.5}$ mass concentration during the entire pregnancy, but the heterogeneity test indicated a significant heterogeneity among the 19 included studies (Q = 112.58, P < 0.001). The trimester-specific analysis showed a stronger meta-estimate of the

Table 2
Pooled associations between $PM_{2.5}$ exposure (per 10 μg/m^3 increment) during pregnancy and change in birth weight (g, 95% CI) in different subgroups.

Subgroups	No. of studies	P for heterogeneity test	Summary β (95% CI)	P for hypothesis test	I^2 (%)	P for Egger's test
Exposure during the entire pregnancy	17	<0.001	−15.9* (−26.8, −5.0)	0.004	98.5	0.921
Trimester specific						
First trimester exposure	11	<0.001	−8.3 (−17.0, 0.4)	0.061	89.8	0.699
Second trimester exposure	10	<0.001	−12.6* (−21.7, −3.1)	0.009	92.2	0.048
Third trimester exposure	13	<0.001	−10.0* (−16.6, −3.5)	0.003	85.8	0.121
Exposure assessment method¶						
Individual level	4	<0.001	−15.7 (−42.1, 10.6)	0.241	87.4	0.825
Semi-individual level	8	0.001	−15.2* (−20.7, −9.7)	<0.001	76.3	0.319
Regional level	6	<0.001	−17.3 (−43.4, 8.8)	0.193	97.7	0.842
Study design¶						
Prospective studies	2	0.454	−11.6 (−28.7, 5.3)	0.176	0.0	–-
Retrospective studies	15	<0.001	−16.7* (−28.7, −4.8)	0.006	98.8	0.862
Country¶						
USA	13	<0.001	−18.8* (−31.4, −6.3)	0.003	99.0	0.648
Others	4	0.401	−1.8 (−12.2, 8.7)	0.742	26.2	0.777

−: The Egger's test could not be fit due to the small number of studies.
¶: All of these subgroup analyses were conducted for the studies that assessed the effects of $PM_{2.5}$ exposure during the entire pregnancy on birth weight. All of these estimates were change in birth weight (g) for each 10 μg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy.
β indicates the change in birth weight (g, 95% CI).
*: $p < 0.05$.

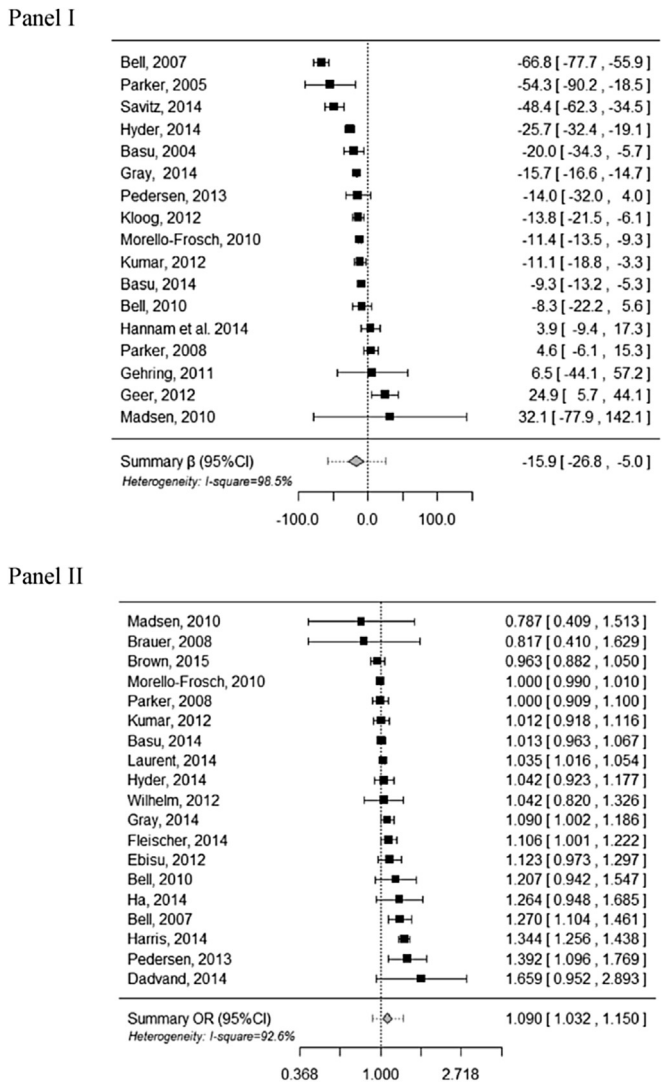

Fig. 2. Forest plots for the pooled associations of $PM_{2.5}$ exposure (per 10 μg/m^3 increment) during the entire pregnancy with birth weight and LBW. Panel I: Pooled estimate of $PM_{2.5}$ exposure on birth weight. β indicates the change in birth weight (g, 95% CI). Panel II: Pooled estimate of $PM_{2.5}$ exposure on LBW.

effect of $PM_{2.5}$ exposure in the third trimester (OR = 1.233, 95% CI: 0.960, 1.585) than that in the first (OR = 1.026, 95% CI: 0.933, 1.130) and second (OR = 1.035, 95% CI: 0.952, 1.125) trimesters, although none of the three estimates were statistically significant. Other subgroup analyses showed significant pooled estimates of $PM_{2.5}$ exposure during the entire pregnancy in the studies that assessed $PM_{2.5}$ exposure at an individual level (OR = 1.431, 95% CI: 1.149, 1.783) and at a regional level (OR = 1.145, 95% CI: 1.061, 1.235), in prospective studies (OR = 1.359, 95% CI: 1.102, 1.676), in retrospective studies (OR = 1.078, 95% CI: 1.022, 1.137), and in studies that were conducted in the USA (OR = 1.079, 95% CI: 1.018, 1.143) and other countries (OR = 1.141, 95% CI: 1.044, 1.247). In particular, in the subgroup meta-analysis that assessed the effects of $PM_{2.5}$ exposure at an individual level, only two studies were included, and their ORs in the LBW risk analysis were 1.392 (95% CI: 1.096, 1.169) and 1.659 (95% CI: 0.952, 2.893) which were quantitatively close to the pooled estimated (OR = 1.431, 95% CI: 1.149, 1.783), (Fig. 2 and Table 3). The results of the meta-regression analyses also demonstrated that the effect estimate of PM2.5 exposure on LBW was significantly impacted by the exposure assessment methods used (β = 0.13, 95% CI: 0.06, 0.20) (Appendix Fig. A.2).

3.4. Pooled estimates of $PM_{2.5}$ chemical constituents on birth weight and LBW

Fig. 3 shows the pooled estimates of the exposure of $PM_{2.5}$ chemical constituents during the entire pregnancy on birth weight and LBW. Birth weight was negatively associated with zinc (Zn), nickel (Ni), titanium (Ti), vanadium (V), organic carbon (OC), nitrate (NO_3^-) and elemental carbon (EC) levels. For example, a 10 ng/m^3 increase in Zn exposure was associated with a 7.5 g (95% CI: 5.0, 10.0) decrease in birth weight. Similarly, the LBW risk was positively associated with potassium (K), zinc, nickel, titanium, elemental carbon, silicon (Si), sulfur (S) and ammonium ion (NH_4^+) levels. For instance, a 10 ng/m^3 increase in Ti exposure was related to a 15.9% (95% CI: 0.7, 33.3) increase in the risk of LBW. The detailed information can be seen in appendix table A.1.

3.5. Sensitivity analyses and publication bias analyses

The meta-analyses were generally robust to the exclusion of single studies that had the largest and smallest effect size with

Table 3
Pooled associations between $PM_{2.5}$ exposure (per 10 μg/m^3 increment) during the pregnancy and LBW risk (OR, 95% CI) in different subgroups.

Subgroups	No. of studies	P for heterogeneity test	Summary OR (95% CI)	P for hypothesis test	I^2 (%)	P for Egger's test
Exposure during the entire pregnancy	19	<0.001	1.090* (1.032, 1.150)	0.002	92.6	0.027
Trimester specific						
First trimester exposure	7	<0.001	1.026 (0.93, 1.130)	0.593	86.9	0.284
Second trimester exposure	7	<0.001	1.035 (0.952, 1.125)	0.421	79.8	0.868
Third trimester exposure	8	<0.001	1.233 (0.960, 1.585)	0.101	98.7	0.045
Exposure assessment method¶						
Individual level	2	0.570	1.431* (1.149, 1.783)	0.001	0.0	–
Semi-individual level	10	0.093	1.008 (0.999, 1.016)	0.074	40.5	0.667
Regional level	8	<0.001	1.145* (1.061, 1.235)	0.001	73.6	0.519
Study design¶						
Prospective studies	3	0.269	1.359* (1.102, 1.676)	0.004	0.1	0.710
Retrospective studies	16	<0.001	1.078* (1.022, 1.137)	0.006	93.1	0.053
Country¶						
USA	14	<0.001	1.079* (1.018, 1.143)	0.010	94.3	0.056
Others	5	0.140	1.141* (1.044, 1.247)	0.004	36.1	0.906

–: The Egger's test could not be fit due to the small number of studies.
¶: All of these subgroup analyses were conducted for the studies that assessed the effects of $PM_{2.5}$ exposure during the entire pregnancy on LBW risks. All of these estimates were ORs for each 10 μg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy.
*: $p < 0.05$.

regard to the significance of the estimated associations, but there was one exception (appendix Fig. A.3 and appendix Fig. A.4). The pooled effect estimate ($\beta = -8.3$ g, 95% CI: −17.0, 0.4) for birth weight with a 10 μg/m^3 increase in $PM_{2.5}$ exposure during the first trimester became statistically significant ($\beta = -9.6$ g, 95% CI: −18.4, −0.7) after excluding the study with the smallest effect size. In addition, to test the influence of studies that considered preterm low birth weight (PLBW), we excluded these three studies and found that the pooled estimate was not significantly changed (OR = 1.078, 95% CI: 1.012, 1.149).

The results of Egger's tests showed that there was no significant publication bias in most of the meta-analyses except for the birth weight analysis of $PM_{2.5}$ exposure during the second trimester and the LBW analyses for $PM_{2.5}$ exposure during the entire pregnancy as well as in the third trimester (Table 2, Table 3, appendix Fig. A.5 and appendix Fig. A.6).

4. Discussion

In this meta-analysis, we collected 32 eligible studies, and quantitatively assessed the associations of the $PM_{2.5}$ mass concentration and its major chemical constituents with birth weight and LBW risk. Our results indicated that maternal $PM_{2.5}$ exposure during pregnancy was associated with a decrease in birth weight and an increased risk of LBW, which is consistent with the results of the previous meta-analyses (Dadvand et al., 2013; Sapkota et al., 2012; Stieb et al., 2012; Zhu et al., 2014). Zhu et al. reported that a 10 μg/m^3 increase in $PM_{2.5}$ exposure over the entire pregnancy was associated with a 14.6 g (95% CI: 9.86, 19.31) decrease in birth weight and a 5.0% (95% CI: 2.0%, 7.0%) increase in LBW risk (Zhu et al., 2014). Stieb et al.'s meta-analysis found a significant association of $PM_{2.5}$ exposure with birth weight ($\beta = -23.4$ g, 95% CI: −45.5, −1.4) and a positive but borderline significant association with LBW risk (OR = 1.05, 95% CI: 0.99, 1.12) (Stieb et al., 2012). Dadvand et al. also estimated a pooled OR of 1.10 (95% CI = 1.03, 1.18) for term LBW per 10 μg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy (Dadvand et al., 2013). These robust results further reveal the toxic effect of $PM_{2.5}$ exposure during pregnancy on fetal growth. Air pollution is ubiquitous. All pregnant women are exposed to it at some level, and immature fetuses are more susceptible to air pollution because they are in critical periods of organogenesis (Backes et al., 2013). Therefore, it is crucial to improve fetal health by decreasing the ambient $PM_{2.5}$ pollution and reducing the maternal $PM_{2.5}$ exposure during pregnancy.

The question of which gestational windows are more susceptible to air pollution is still a controversial issue, and the results of previous studies are inconsistent (Gehring et al., 2011; Gray et al., 2014; Mannes et al., 2005). In this study, the significant associations between a decreased birth weight and $PM_{2.5}$ exposures in the second and third trimester indicate that the late pregnancy might be the critical exposure window, which is also supported by the stronger effect of $PM_{2.5}$ exposure during the third trimester on the risk of LBW. Our results are consistent with the findings of studies that assessed the negative effects of PM_{10} and smoking on birth weight (Lieberman et al., 1994; Mannes et al., 2005). The specific triggering events in late pregnancy remain unclear, but some hypotheses from previous studies may provide clues. The implantation of the fetus and the formation of the placenta occur during the first trimester, and it has been proposed that higher $PM_{2.5}$ exposure during this period might cause genetic mutations and hence increase the risks of fetal malformation, miscarriage and even death (Lin and Santolaya-Forgas, 1998). These serious harmful effects might attenuate the association between $PM_{2.5}$ exposure in early pregnancy and birth weight. In contrast, fetal weight gain mainly occurs in the third trimester, during which $PM_{2.5}$ exposure might mainly lead to fetal growth retardation and weight loss. In addition, the data in most of the studies included in this meta-analysis were collected from birth certificate information systems, which may have resulted in the misclassification of gestational age and $PM_{2.5}$ exposure assessment. Assignment of the exposures according to birth address might be less accurate for early pregnancy exposures than for later pregnancy exposures due to recall bias and maternal mobility during pregnancy. This may bias the early pregnancy effect estimates towards the null (Sapkota et al., 2012).

To test the sources of heterogeneity among the included studies, several subgroup analyses were conducted. Our results showed a stronger pooled association between $PM_{2.5}$ exposure and LBW in the studies that assessed $PM_{2.5}$ exposure at the individual level than at the semi-individual or regional levels. It has been suggested that $PM_{2.5}$ exposure assessment at the semi-individual and regional levels may result in a misrepresentation of the exposure because these methods do not account for the spatial misalignment between an individual's residence and monitoring sites and ignore the fact that individuals have different activity modes (indoor and outdoor activity time) and may change their residential address during pregnancy (Berrocal et al., 2011; Brauer et al., 2008; Zeger et al., 2000). In contrast, the individual level assessment method included variables that affect people's $PM_{2.5}$ exposure, including

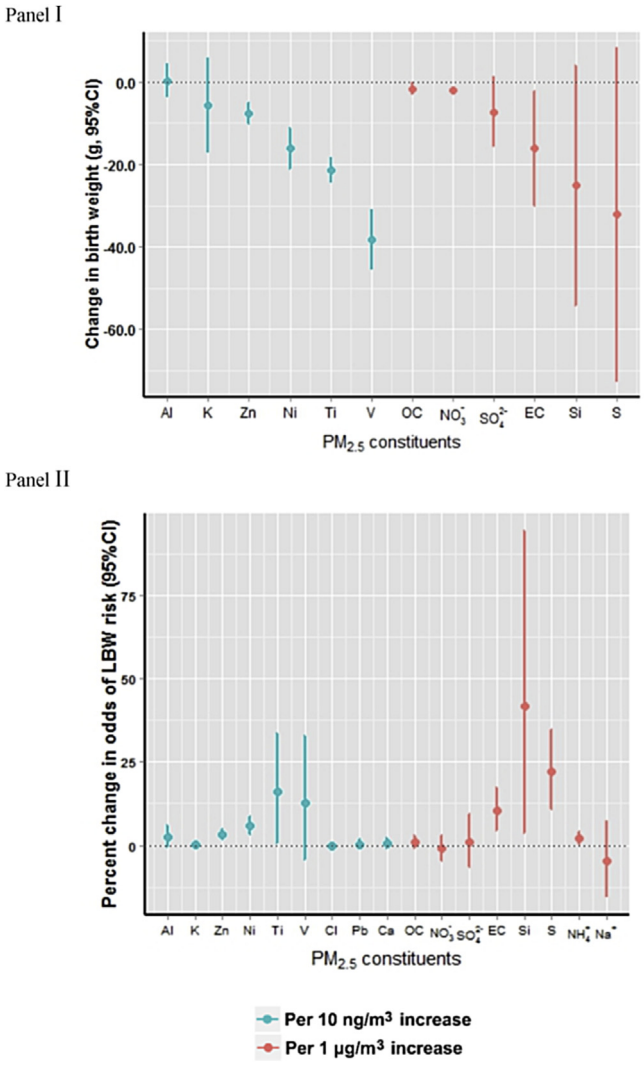

Fig. 3. Pooled estimates of exposure to $PM_{2.5}$ constituents during the entire pregnancy on change in birth weight (g) and LBW risk. Panel I: Changes in birth weight (g, 95%CI) for per unit increase in $PM_{2.5}$ constituents, in which aluminum (Al), potassium (K), zinc (Zn), nickel (Ni), titanium (Ti) and vanadium (V) were measured using 10 ng/m^3 as the unit increase, and organic carbon (OC), nitrate (NO_3^-), sulfate (SO_4^{2-}), elemental carbon (EC), silicon (Si) as well as sulfur (S) were measured by using 1 μg/m^3 as the unit increase. Panel II: Percent change in the odds for LBW (95% CI) for per unit increase in $PM_{2.5}$ constituents, in which aluminum (Al), potassium (K), zinc (Zn), nickel (Ni), titanium (Ti), vanadium (V), chlorine (Cl), lead (Pb) and calcium (Ca) were measured using 10 ng/m^3 as the unit increase, and organic carbon (OC), nitrate (NO_3^-), sulfate (SO_4^{2-}), elemental carbon (EC), silicon (Si), sulfur (S), ammonium ion (NH_4^+) as well as sodium ion (Na^+) were measured using 1 μg/m^3 as the unit increase.

traffic, meteorology, roadway geometry, vehicle emission, air quality monitoring data, and land use information (Gehring et al., 2011; Wu et al., 2009). Some recent studies have even used personal monitors to assess maternal individual level exposure to $PM_{2.5}$ (Jedrychowski et al., 2009). This method was shown to greatly reduce the bias in the exposure assessment. However, we did not find a statistically significant association between birth weight as a continuous variable and $PM_{2.5}$ exposure at the individual level. The small number of included studies ($n = 4$) may be one reason for the lack of significance, and the significant between-study heterogeneity between these four studies may also play a role.

It is well known that the toxicity and health impacts of $PM_{2.5}$ may vary by geographic region if the sources of $PM_{2.5}$ differ (Laden et al., 2000; Wilhelm et al., 2011). Therefore, it is reasonable to conduct subgroup meta-analyses to test the variation in the $PM_{2.5}$ estimates between regions. In this study, we divided all of the included studies into two groups (USA and other countries), because most of the included studies were conducted in the USA. For the birth weight analyses, we observed a statistically significant pooled estimate of the effects of $PM_{2.5}$ for the US studies but a non-significant estimate for the studies in other countries. For the LBW analyses, significant estimates of $PM_{2.5}$ exposure effects were found in both groups. This discrepancy may be partially related to the differences in the populations, environment, or $PM_{2.5}$ constituents between regions (Harris et al., 2014). Moreover, the small number of studies included in the second group may be another important factor. For example, only four studies were available in the meta-analysis of $PM_{2.5}$ exposure and birth weight, which may limit the statistical power. Therefore, more studies in counties other than the USA are needed, especially in middle or low income counties with heavier air pollution. For example, only one study was found that was conducted simultaneously in China and India to assess the estimate of $PM_{2.5}$ on LBW. These two countries have very severe $PM_{2.5}$ pollution (Van Donkelaar et al., 2010). Dadvand et al. observed that higher median $PM_{2.5}$ exposure levels seemed to have a stronger adverse effect on LBW (Dadvand et al., 2013). Therefore, studies in these countries could provide important information for policy makers and public health practitioners to reduce the health impacts of air pollution.

In addition, $PM_{2.5}$ is a mixture of multiple inorganic and organic constituents, and its health effects can vary depending on different constituents and origins (Habre et al., 2014; Kelly and Fussell, 2012). Therefore, estimating the individual health impact of major $PM_{2.5}$ chemical constituents may be useful. In this study, our findings indicated a large range of variation in birth weight-reducing effects among the $PM_{2.5}$ chemical constituents. For instance, birth weight was negatively associated with zinc, nickel, titanium, vanadium, organic carbon, nitrate and elemental carbon, which might indicate their toxic effects were larger than those of other constituents. Furthermore, we also found borderline effects of some constituents, such as sulfate and silicon. Their statistical power might be limited by the small number of studies. The biological mechanisms of $PM_{2.5}$ affecting birth weight are not well understood. Particulate matter might lead to pulmonary inflammation in the mother, which can reduce the levels of oxygen available to the fetus, and the placental inflammation can also impair gas and nutrition exchange. In particular, some constituents, such as metals and PAHs, in $PM_{2.5}$ may cause oxidative stress and result in DNA damage to the fetus itself. In addition, metals can also accumulate in fetal tissues and may influence fetal growth at high levels of exposure (Basu et al., 2004; Bell et al., 2010, 2010, 2012; Ebisu and Bell, 2012).

The limitations of this meta-analysis are that, we found high or moderate heterogeneities in most of the subgroup meta-analyses, although less heterogeneity was found in some subgroups. These findings indicate that the heterogeneity among the included studies may also have been affected by other factors, such as socioeconomic status, that we did not consider in this study due to the limited number of relevant studies. Therefore, further meta-analyses are necessary to explore the sources of heterogeneity as more original studies are conducted in the future.

5. Conclusions

In summary, this meta-analysis observed a clear association between $PM_{2.5}$ exposure during pregnancy and decreased birth weights, and late pregnancy might be the critical window for these adverse effects. Some specific $PM_{2.5}$ constituents may have more severe harmful effects on fetal weight. The exposure assessment

methods, study designs and study settings, are important sources of the heterogeneity between the included studies. These results extend our understanding of the adverse effects of $PM_{2.5}$ on fetal health, and emphasize that it is crucial to reduce the ambient $PM_{2.5}$ pollution and reduce maternal $PM_{2.5}$ exposure during pregnancy to improve birth outcomes. More studies are needed in the future to further assess the adverse effects of $PM_{2.5}$ on fetal health in countries other than the USA, especially in developing countries.

Declaration of interests

We declare that we have no competing interests.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81502819), Natural Science Foundation of Guangdong Province (2015A030310220), Fundamental Research Funds for the Central Universities (12ykpy13) and Postdoctoral Science Foundation of China (2013M542230).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2015.12.022.

References

Backes, C.H., Nelin, T., Gorr, M.W., Wold, L.E., 2013. Early life exposure to air pollution: how bad is it? Toxicol. Lett. 216, 47–53.
Basu, R., Harris, M., Sie, L., Malig, B., Broadwin, R., Green, R., 2014. Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California. Environ. Res. 128, 42–51.
Basu, R., Woodruff, T.J., Parker, J.D., Saulnier, L., Schoendorf, K.C., 2004. Comparing exposure metrics in the relationship between PM2. 5 and birth weight in California. J. Expo. Sci. Env. Epidemiol 14, 391–396.
Bell, M.L., Belanger, K., Ebisu, K., Gent, J.F., Leaderer, B.P., 2012. Relationship between birth weight and exposure to airborne fine particulate potassium and titanium during gestation. Environ. Res. 117, 83–89.
Bell, M.L., Belanger, K., Ebisu, K., Gent, J.F., Lee, H.J., Koutrakis, P., Leaderer, B.P., 2010. Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. Epidemiology 21, 884–891.
Bell, M.L., Ebisu, K., Belanger, K., 2007. Ambient air pollution and low birth weight in Connecticut and Massachusetts. Environ. Health Perspect. 1118–1124.
Bell, M.L., Ebisu, K., Belanger, K., 2008. The relationship between air pollution and low birth weight: effects by mother's age, infant sex, co-pollutants, and preterm births. Environ. Res. Lett. 3, 044003.
Berrocal, V.J., Gelfand, A.E., Holland, D.M., Burke, J., Miranda, M.L., 2011. On the use of a PM2. 5 exposure simulator to explain birthweight. Environmetrics 22, 553–571.
Brauer, M., Lencar, C., Tamburic, L., Koehoorn, M., Demers, P., Karr, C., 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ. Health Perspect. 116, 680.
Brown, J.M., Harris, G., Pantea, C., Hwang, S.-A., Talbot, T.O., 2015. Linking air pollution data and adverse birth outcomes: environmental public health tracking in New York state. J. Public Health Manag. Pract. 21, S68–S74.
Dadvand, P., Ostro, B., Figueras, F., Foraster, M., Basagaña, X., Valentín, A., Martinez, D., Beelen, R., Cirach, M., Hoek, G., 2014. Residential proximity to major roads and term low birth weight: the roles of air pollution, heat, noise, and road-adjacent trees. Epidemiology 25, 518–525.
Dadvand, P., Parker, J., Bell, M.L., Bonzini, M., Brauer, M., Darrow, L.A., Gehring, U., Glinianaia, S.V., Gouveia, N., Ha, E.-h, 2013. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ. Health Perspect. 121, 267–373.
Darrow, L.A., Klein, M., Strickland, M.J., Mulholland, J.A., Tolbert, P.E., 2011. Ambient air pollution and birth weight in full-term infants in Atlanta, 1994-2004. Environ. Health Perspect. 119, 731–737.
Ebisu, K., Bell, M.L., 2012. Airborne PM2.5 chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States. Environ. Health Perspect. 120, 1746–1752.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634.
Fleischer, N.L., Merialdi, M., van Donkelaar, A., Vadillo-Ortega, F., Martin, R.V., Betran, A.P., Souza, J.P., 2014. Outdoor air pollution, preterm birth, and low birth weight: analysis of the world health organization global survey on maternal and perinatal health. Environ. Health Perspect. 122, 425–430.
Geer, L.A., Weedon, J., Bell, M.L., 2012. Ambient air pollution and term birth weight in Texas from 1998 to 2004. J. Air Waste Manag. Assoc. 62, 1285–1295.
Gehring, U., Wijga, A.H., Fischer, P., de Jongste, J.C., Kerkhof, M., Koppelman, G.H., Smit, H.A., Brunekreef, B., 2011. Traffic-related air pollution, preterm birth and term birth weight in the PIAMA birth cohort study. Environ. Res. 111, 125–135.
Gray, S.C., Edwards, S.E., Schultz, B.D., Miranda, M.L., 2014. Assessing the impact of race, social factors and air pollution on birth outcomes: a population-based study. Environ. Health 13, 4.
Ha, S., Hu, H., Roussos-Ross, D., Haidong, K., Roth, J., Xu, X., 2014. The effects of air pollution on adverse birth outcomes. Environ. Res. 134, 198–204.
Habre, R., Moshier, E., Castro, W., Nath, A., Grunin, A., Rohr, A., Godbold, J., Schachter, N., Kattan, M., Coull, B., 2014. The effects of PM2.5 and its components from indoor and outdoor sources on cough and wheeze symptoms in asthmatic children. J. Expo. Sci. Env. Epidemiol. 24, 380–387.
Hannam, K., McNamee, R., Baker, P., Sibley, C., Agius, R., 2014. Air pollution exposure and adverse pregnancy outcomes in a large UK birth cohort: use of a novel spatio-temporal modelling technique. Scand. J. Work Environ. Health 40, 518–530.
Harris, G., Thompson, W.D., Fitzgerald, E., Wartenberg, D., 2014. The association of PM2.5 with full term low birth weight at different spatial scales. Environ. Res. 134, 427–434.
Higgins, J.P., Green, S., 2008. Cochrane handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, Chichester, UK, pp. 243–293.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560.
Hoek, G., Krishnan, R.M., Beelen, R., Peters, A., Ostro, B., Brunekreef, B., Kaufman, J.D., 2013. Long-term air pollution exposure and cardio-respiratory mortality: a review. Environ. Health 12, 43.
Hyder, A., Lee, H.J., Ebisu, K., Koutrakis, P., Belanger, K., Bell, M.L., 2014. PM2. 5 exposure and birth outcomes: use of satellite-and monitor-based data. Epidemiology 25, 58–67.
Jedrychowski, W., Perera, F., Mrozek-Budzyn, D., Mroz, E., Flak, E., Spengler, J.D., Edwards, S., Jacek, R., Kaim, I., Skolicki, Z., 2009. Gender differences in fetal growth of newborns exposed prenatally to airborne fine particulate matter. Environ. Res. 109, 447–456.
Kelly, F.J., Fussell, J.C., 2012. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. Atmos. Environ. 60, 504–526.
Kloog, I., Melly, S.J., Ridgway, W.L., Coull, B.A., Schwartz, J., 2012. Using new satellite based exposure methods to study the association between pregnancy pm2. 5 exposure, premature birth and birth weight in Massachusetts. Environ. Health 11, 10.1186.
Kumar, N., 2012. Uncertainty in the relationship between criteria pollutants and low birth weight in Chicago. Atmos. Environ. 49, 171–179.
Laden, F., Neas, L.M., Dockery, D.W., Schwartz, J., 2000. Association of fine particulate matter from different sources with daily mortality in six US cities. Environ. Health Perspect. 108, 941–947.
Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J., 2014. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ. Res. 134, 488–495.
Lieberman, E., Gremy, I., Lang, J.M., Cohen, A.P., 1994. Low birthweight at term and the timing of fetal exposure to maternal smoking. Am. J. Public Health 84, 1127–1131.
Lin, C.-C., Santolaya-Forgas, J., 1998. Current concepts of fetal growth restriction: part I. Causes, classification, and pathophysiology. Obstet. Gynecol. 92, 1044–1055.
Madsen, C., Gehring, U., Erik Walker, S., Brunekreef, B., Stigum, H., Næss, Ø., Nafstad, P., 2010. Ambient air pollution exposure, residential mobility and term birth weight in Oslo, Norway. Environ. Res. 110, 363–371.
Mannes, T., Jalaludin, B., Morgan, G., Lincoln, D., Sheppeard, V., Corbett, S., 2005. Impact of ambient air pollution on birth weight in Sydney, Australia. Occup. Environ. Med. 62, 524–530.
Morello-Frosch, R., Jesdale, B.M., Sadd, J.L., Pastor, M., 2010. Ambient air pollution exposure and full-term birth weight in California. Environ. Health 9, 1–13.
Parker, J.D., Woodruff, T.J., 2008. Influences of study design and location on the relationship between particulate matter air pollution and birthweight. Paediatr. Perinat. Ep 22, 214–227.
Parker, J.D., Woodruff, T.J., Basu, R., Schoendorf, K.C., 2005. Air pollution and birth weight among term infants in California. Pediatrics 115, 121–128.
Pedersen, M., Giorgis-Allemand, L., Bernard, C., Aguilera, I., Andersen, A.-M.N., Ballester, F., Beelen, R.M., Chatzi, L., Cirach, M., Danileviciute, A., 2013. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). Lancet Respir. Med. 1, 695–704.
Pope III, C.A., Dockery, D.W., 2006. Health effects of fine particulate air pollution: lines that connect. J. Air Waste Manag. Assoc. 56, 709–742.
Sapkota, A., Chelikowsky, A.P., Nachman, K.E., Cohen, A.J., Ritz, B., 2012. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Qual. Atmos. Health 5, 369–381.
Savitz, D.A., Bobb, J.F., Carr, J.L., Clougherty, J.E., Dominici, F., Elston, B., Ito, K., Ross, Z., Yee, M., Matte, T.D., 2014. Ambient fine particulate matter, nitrogen dioxide, and term birth weight in New York, New York. Am. J. Epidemiol. 179, 457–466.
Stieb, D.M., Chen, L., Eshoul, M., Judek, S., 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111.

Trasande, L., Wong, K., Roy, A., Savitz, D.A., Thurston, G., 2013. Exploring prenatal outdoor air pollution, birth outcomes and neonatal health care utilization in a nationally representative sample. J. Expo. Sci. Environ. Epidemiol. 23, 315–321.
Van Donkelaar, A., Martin, R.V., Brauer, M., Kahn, R., Levy, R., Verduzco, C., Villeneuve, P.J., 2010. Global estimates of ambient fine particulate matter concentrations from satellite-based aerosol optical depth: development and application. Environ. Health Perspect. 118, 847–855.
Vinikoor-Imler, L.C., Davis, J.A., Meyer, R.E., Messer, L.C., Luben, T.J., 2014. Associations between prenatal exposure to air pollution, small for gestational age, and term low birthweight in a state-wide birth cohort. Environ. Res. 132, 132–139.
Wilhelm, M., Ghosh, J.K., Su, J., Cockburn, M., Jerrett, M., Ritz, B., 2011. Traffic-related air toxics and preterm birth: a population-based case-control study in Los Angeles County, California. Environ. Health 10, 1–12.
Wilhelm, M., Kay Ghosh, J., Su, J., Cockburn, M., Jerrett, M., Ritz, B., 2012. Traffic-related air toxics and term low birth weight in Los Angeles County, California. Environ. Health Perspect. 120, 132–138.
Wu, J., Ren, C., Delfino, R.J., Chung, J., Wilhelm, M., Ritz, B., 2009. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ. Health Perspect. 117, 1773–1779.
Zeger, S.L., Thomas, D., Dominici, F., Samet, J.M., Schwartz, J., Dockery, D., Cohen, A., 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108, 419–426.
Zhu, X., Liu, Y., Chen, Y., Yao, C., Che, Z., Cao, J., 2014. Maternal exposure to fine particulate matter (PM) and pregnancy outcomes: a meta-analysis. Environ. Sci. Pollut. Res. 22, 3397–3399.