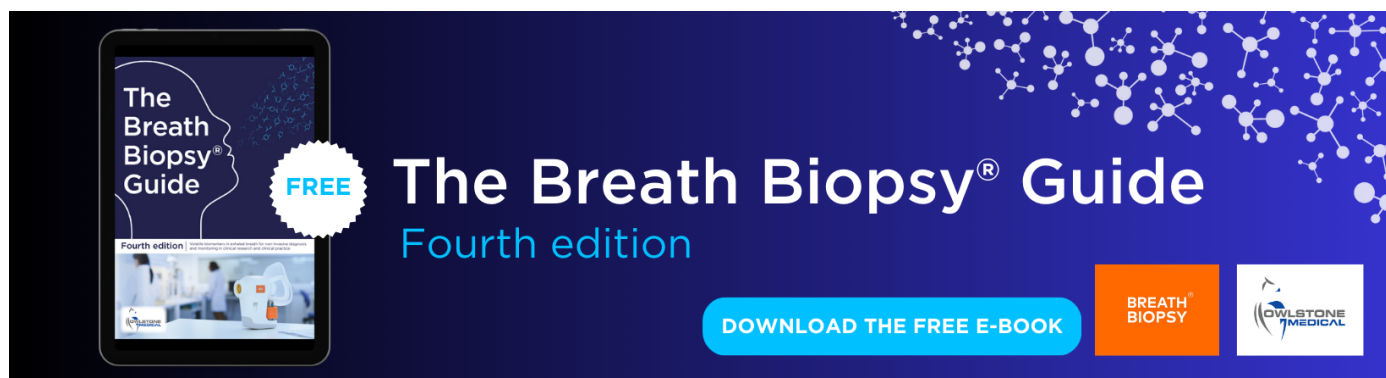**TOPICAL REVIEW • OPEN ACCESS**

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To cite this article: Seulkee Heo *et al* 2019 *Environ. Res. Lett.* **14** 123004

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Environmental Research Letters

TOPICAL REVIEW

Risk of particulate matter on birth outcomes in relation to maternal socio-economic factors: a systematic review

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Abstract

A growing number of studies provide evidence of an association between exposure to maternal air pollution during pregnancy and adverse birth outcomes including low birth weight (LBW) and preterm birth. Prevention of these health effects of air pollution is critical to reducing the adverse infant outcomes, which can have impacts throughout the life course. However, there is no consensus on whether the association between air pollution exposure and birth outcomes varies by maternal risk factors including demographic characteristics and socio-economic status (SES). Such information is vital to understand potential environmental health disparities. Our search found 859 unique studies, of which 45 studies met our inclusion criteria (January 2000–July 2019). We systematically reviewed the 45 identified epidemiologic studies and summarized the results on effect modifications by maternal race/ethnicity, educational attainment, income, and area-level SES. We considered adverse birth outcomes of preterm birth, LBW, small for gestational age (SGA), and stillbirth. Suggestive evidence of higher risk of particulate matter (PM) in infants of African–American/black mothers than infants of other women was found for preterm birth and LBW. We found weak evidence that PM risk was higher for infants of mothers with lower educational attainment for preterm birth and LBW. Due to the small study numbers, we were unable to conclude whether effect modification is present for income, occupation, and area-level SES, and additional research is needed. Furthermore, adverse birth outcomes such as SGA and stillbirth need more study to understand potential environmental justice issues regarding the impact of PM exposure during pregnancy on birth outcomes.

1. Introduction

Birth outcomes such as low birth weight (LBW) (<2500 g) and preterm birth (PTB) (live birth before 37 weeks of pregnancy), like cardiovascular and respiratory diseases, have been identified as risks associated with exposure to ambient air pollution. These outcomes can further lead to neonatal mortality and physical morbidity (Class *et al* 2014). Low birth weight and preterm birth have serious health consequences through the life course, including developmental disability, obesity, hypertension, diabetes, heart disease, and psychiatric problems (Brauer *et al* 2008, Blumenshine *et al* 2010). The World Health Organization estimated that in 2014 approximately

10.6% of all live births globally were preterm (Chawanpaiboon *et al* 2019), which highlights the need of enhanced understanding of maternal and infant health risk factors.

Numerous epidemiologic studies have investigated the link between prenatal exposure to air pollution and adverse birth outcomes. Some previous review studies reported that evidence is sufficient for such relationships; a review based on 62 epidemiologic studies reported that the evidence is robust for the relationship between birth outcomes including LBW and PTB and ambient concentration of particulate matter (PM), CO, and NO_2, while the evidence was less consistent for ozone and SO_2 (Stieb *et al* 2012). Another review study suggested evidence of a potential

effect of exposure to PM, especially PM with aerodynamic diameter no larger than 2.5 μm (PM$_{2.5}$), on LBW (Bonzini *et al* 2010). Although review studies are few, some studies suggested that the evidence of the impact of PM was the most robust for LBW compared to other outcomes such as small for gestational age (SGA, birth weight <10th percentile for gestational age and sex) or PTB (Šrám *et al* 2005, Stieb *et al* 2012). These previous findings imply that preventing the health effects of air pollution is critical to improving infant health and to reducing the disease burden from adverse birth outcomes.

Studies have documented and quantified racial/ethnic inequity in the level of exposure to fine PM and consumption of goods and services in the United States (Tessum *et al* 2019). Several studies in other countries such as China have shown that people with lower socio-economic status (SES) are at higher risk of exposure to air pollution (Li *et al* 2018, Ma *et al* 2019). Other studies found that risk of PM differs across regions and populations due to demographic or socio-economic factors (Bell *et al* 2014). Review articles have mainly focused on examination of different associations between air pollution and adverse birth outcomes regarding particular exposure periods (e.g. trimester), air pollutants, and type of exposure variables (e.g. continuous, dichotomous, categorical) (Stieb *et al* 2012, Jacobs *et al* 2017). Consensus does not exist on effect modification of the relationship between air pollution and birth outcomes by maternal risk factors including demographic variables and SES. Examining which populations are most impacted by associations between PM and adverse birth outcomes can have implications for the strategies to reduce the disparities from air pollution.

We conducted a systematic review for published epidemiologic studies and summarized evidence of potential effect modification of maternal race/ethnicity and SES factors on the associations between PM exposure during pregnancy and risk of adverse birth outcomes including LBW, SGA, PTB, and stillbirth. Our review illuminates current research gaps and can inform decision-making in public health and environmental justice concerns.

2. Materials and methods
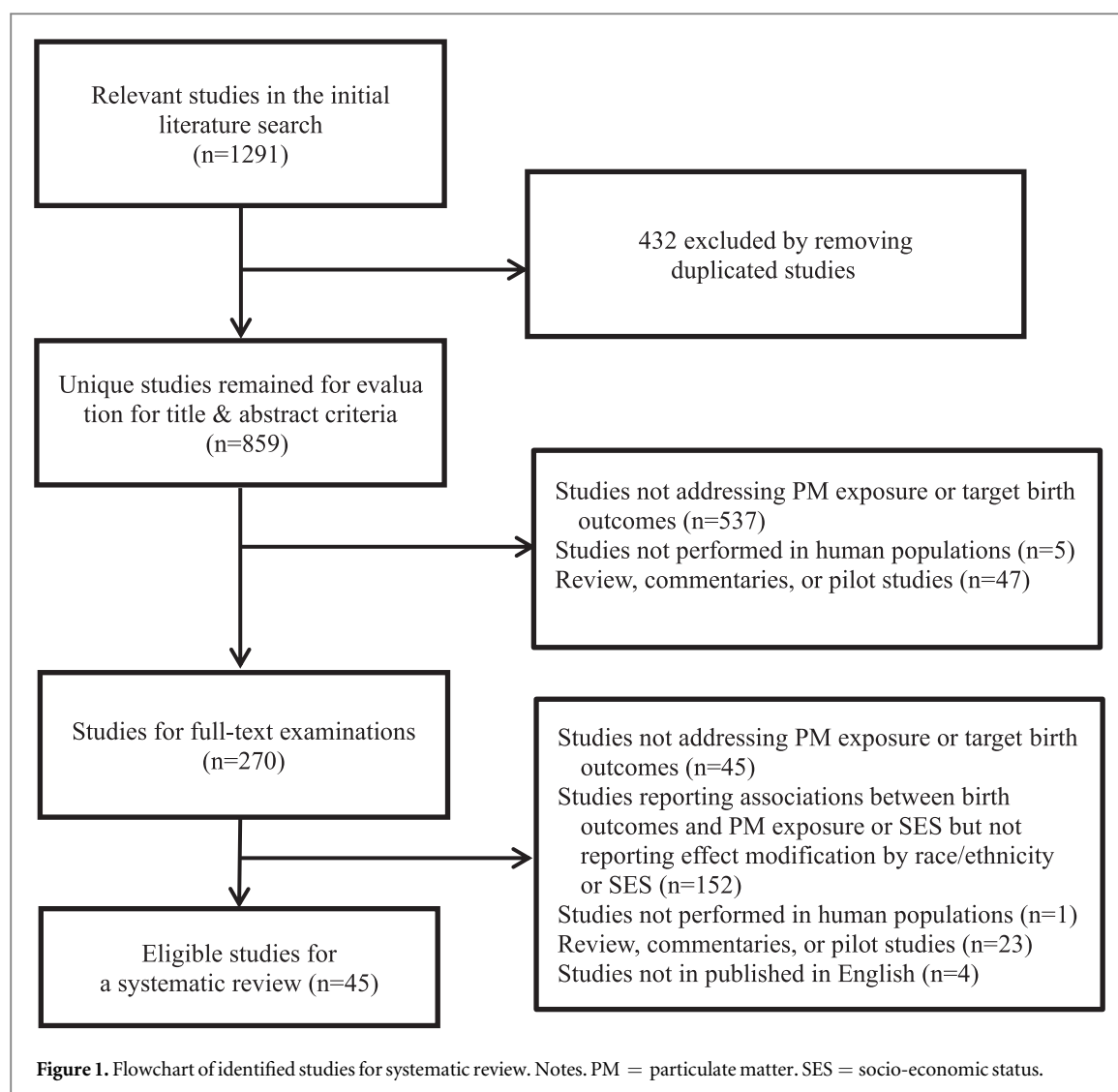
2.1. Literature search
Search terms and inclusion/exclusion criteria were designed to identify population-based studies for effect modification of race/ethnicity and/or SES on PM exposure and target birth outcomes. Literature searches were conducted for epidemiologic studies including non-randomized designs (i.e. cohort study, case-control study, cross-sectional study, economic study, time-series analysis) that examined the impact of PM with aerodynamic no larger than 10 μm (PM$_{10}$) or PM$_{2.5}$, on birth outcomes published from January

2000 to July 2019. We limited our search for papers published in English. Targeted birth outcomes were PTB, LBW, SGA, and stillbirth. We conducted the searches in the Medline/PUBMED (National Institutes of Health 2019) database. The titles, abstracts, and keywords were searched using the combination of following terms in order to identify the required articles: 'air pollution', 'PM$_{10}$', 'PM$_{2.5}$', 'air pollutant', 'particulate', 'case control', 'cohort', 'pregnancy', 'birth outcome', 'stillbirth', 'birth weight', 'low birth weight', 'preterm birth', 'effect modi*', 'SES', 'socioeconomic', 'income', and 'race'. The truncation filter 'asterisks (*)' were used with the search terms to search all terms that begin with a certain combination of letters but can have any combination of letters representing the asterisk (e.g. modi* can be modification, modify, etc). The specific search strategies used in Medline/PUBMED searches are shown in our PICOS Worksheet and Search Strategy (see online supplementary materials available online at stacks.iop.org/ERL/14/123004/mmedia). Studies identified in each search strategy were combined and deduplicated.

We screened the titles and abstracts to exclude studies that are not related to our research question. The included studies fulfilled all of the following inclusion criteria: (1) examined maternal exposure to PM (PM$_{10}$, PM$_{2.5}$ and/or smaller PM) during pregnancy; (2) included at least one of the birth outcomes of PTB, LBW, SGA, and stillbirth; and (3) provided risk estimations of PM and birth outcomes modified by maternal race/ethnicity and/or SES. Exclusion criteria included (1) studies not addressing PM exposure or target birth outcomes; (2) studies not reporting effect modification; (3) studies not performed in human populations; (4) conference abstracts, brief research paper without study details, review, commentaries, or pilot studies; and (5) epidemiologic studies not falling into non-randomized study (e.g. disease mapping study). A flow chart of study identification steps is shown figure 1. We reviewed the whole text of each identified study deserving full-text review and systematic review, as shown in figure 1.

2.2. Data extraction
For the identified relevant studies, we extracted the following information: study location, study duration, population size, study design, pollutants considered, exposure time windows, type of birth outcomes, type of effect modifiers and definition, type of statistical models for effect modifications (e.g. application of interaction terms or stratification), increment of pollution for estimates of the association (e.g. 10 μg m^{-3}), risk estimates and associated uncertainty (e.g. odds ratios (ORs) or relative risks (RRs) and 95% CIs), maternal and/or paternal risk factors considered for adjustment, and data source for exposure. Two investigators independently processed the data extraction from each study using the same data extraction

Figure 1. Flowchart of identified studies for systematic review. Notes. PM = particulate matter. SES = socio-economic status.

form. Effect modifiers were identified when a study provided different risk estimates of the relationship between PM and birth outcomes for the level or categories of maternal risk factors. When the study reported differences by maternal race/ethnicity or SES only for PM exposure level or prevalence of birth outcomes, but did not investigate potential differences in the exposure-response relationships between PM and the risk of birth outcomes, no effect modifier of the association between PM and adverse birth outcome was confirmed from such studies. While we consider multiple exposure time windows for the current systematic review, we extracted associations, if available, for exposure throughout whole pregnancy or trimester-specific periods. We identified each potential SES modifier as individual-level maternal SES or area-level SES. If a study provided stratified estimates for the association between exposure and birth outcomes by level of SES, we extracted each of stratified estimates. We determined that not enough studies were available to conduct quantitative meta-analysis due to the small number of identified studies for each SES factor and their sub-groups and varied

study designs. Instead, we provide a narrative summary and qualitative assessment.

2.3. Systematic review

The systematic review was performed with consideration of guideline tools for assessing quality of population-based health studies and the methods applied by previous review studies (Bell *et al* 2014). To summarize study characteristics, we referred to quality criteria from the assessment tools of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), the Quality Assessment Tool for review articles by the Health Evidence (Health Evidence 2018), Cochrane guideline (Handbook version 5.1) (Higgins and Green 2011), and the Quality Assessment Tool for Quantitative Studies (National Collaborating Centre for Methods and Tools 2017) regarding the characteristics of primary studies and our research question of systematic review. As a result, we summarized study characteristics of identified studies for the following areas: description of research design and population size, sources of exposure and health data, clear definition of all exposure variables,

health outcomes, race/ethnicity and SES factors, description of exposure time window and statistical models (e.g. logistic model, linear regression) use of sensitivity analysis and presentation of associated results (e.g. tables, figures), and exposure assessment methods (e.g. nearest monitors, modeling estimates). For description of study design, we identified whether a given study stated use of the following methods: ecologic, time-series, cross-sectional, cohort, case-control, or case-crossover. Then, we assigned the study design based on the health data source and statistical analysis used in each study. A study was assigned the category of 'cohort' study only when study participants were followed for the period of pregnancy. When the health outcomes of infants were identified using a pre-existing health data source such as birth registry, the study was identified as a 'case-control' study in this review, although the study in question considered its study population as a birth cohort. We recognize that terms in epidemiology are not used with perfect consistency, and our goal is to use them consistently within this review.

We summarized the evidence of a potential modified association between PM exposure and birth outcomes for each identified effect modifier using methods adapted from the established categorization methods by Institute of Medicine committees (Fulco *et al* 2000) and applied by the US Congress and previous studies (Bell *et al* 2013). We used categories of no, weak, suggestive, and strong evidence of evidence of effect modification. The assignment of these categories for each effect modifier was conducted based on the quantity and quality of the reported results. The quality of results was based on the statistical uncertainty for the relationships between exposure to PM and birth outcomes by status of effect modifiers, although we recognize that overall quality reflects many other aspects of a study. It should be noted that the summarized strengths of effect modification are not a conclusive synthesis of evidence but a summary of the existing state of scientific evidence and the relative comparisons among the identified 45 studies and the effect modifiers.

3. Results

3.1. Characteristics of the eligible studies
The literature search identified 1291 research papers indexed from 1 January 2000 to 7 July 2019, with 859 unique papers. After exclusion, 45 papers met our inclusion criteria. Table 1 summarizes key study features of the included studies. The majority of identified studies was based on regions in the US (33 of the 45 studies). Of the 45 studies, 23 studies addressed term birth weight as either a continuous measurement (i.e. considering birth weight as a continuous variable) or dichotomous measurement (i.e. term low birth weight (TLBW)), 24 addressed PTB, 11 addressed

SGA, and 3 addressed stillbirth (table 2). Some studies considered multiple health outcomes. $PM_{2.5}$ was the exposure metric for 38 studies with 15 studies considering PM_{10}, and 3 study considered the coarse fraction of PM, defined as PM_{10}–$PM_{2.5}$. Finer particles than $PM_{2.5}$ were considered in 2 studies ($PM_{1.0}$ in 1 study and $PM_{0.1}$ in 1 study) (table 2). In terms of study design, 75.6% of the studies (34 studies) conducted case-control analysis, while 20.0% (9 studies) were based on a cohort design (table 2) (Rudra *et al* 2011, Lee *et al* 2013, Pereira *et al* 2014a, 2014b, Schembari *et al* 2015, Stieb *et al* 2016, Wang *et al* 2018, Sheridan *et al* 2019, Stieb *et al* 2019).

Of the 45 studies that examined effect modification by maternal race/ethnicity and/or SES, the most commonly studied effect modifier was race/ethnicity with 31 studies. One study used race/ethnicity of infants as a potential effect modifier. The other identified effect modifiers were area-level integrated SES (e.g. European deprivation index) by 5 studies, mothers' educational attainment by 17 studies, mothers' occupation (e.g. worked as farmers versus other job workers) by 2 studies, and income or poverty level by 9 studies (table 2).

About 64.4% of the 45 studies analyzed birth outcome risks associated with PM exposure during specific trimesters, while 64.4% of the 45 studies focused on the whole pregnancy. Other exposure periods such as daily or annual exposure was considered for 13 studies, and 2 studies did not specify the exposure period.

Various confounding variables of maternal risk factors were addressed in the estimation between PM and birth outcomes in the identified studies. About 57.8% (26 studies) of the identified studies adjusted for mother's race/ethnicity, 46.7% (21 studies) for maternal smoking use during pregnancy, 31.1% (14 studies) for mothers' marital status, and 46.7% (21 studies) for sex of infant, while most studies (75.6%, 34 studies) adjusted for maternal age. Maternal educational attainment, which can be considered a proxy for SES, was adjusted for in more than half of the studies as well (57.8%, 26 studies).

3.2. Summary of effect modification
The summary of scientific evidence for potential effect modification of the PM-birth outcome association by the selected effect modifiers is shown in the figure 2 and supplementary table S1. For race/ethnicity, all studies investigated effect modification based on the race/ethnicity of the mother except for one study (Smith *et al* 2017). The US was the most represented country among the studies focusing on race/ethnicity. Among 14 studies that focused on LBW and maternal race/ethnicity, 9 studies reported statistically significant risks from PM exposure, with higher risk for infants of African American/black mothers compared to others. Two other studies found that risks for PM exposure, estimated separately by racial/ethnic

Table 1. Studies included in the systematic review.

Study No.	Study	Location	Study period	Population size (No. births)	Study design	Effect modifiers	Air pollutant exposures	Health outcomes
[1]	Basu et al (2014)	California, US	2000–2006	646 296	Case-control	Race/ethnicity, age	$PM_{2.5}$, chemicals	BW, TLBW
[2]	Bell et al (2007)	Connecticut and Massachusetts, US	1999–2002	358 504	Case-control	Race/ethnicity	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO	BW
[3]	Benmarhnia et al (2017)	California, US	2005–2010	1066 783	Case-control	Race/ethnicity, maternal SES (education, age, medical enrollment, missing paternal information), neighborhood SES status (unemployment rate, poverty, linguistic minority, educational attainment)	$PM_{2.5}$, NO_2	PTB, VPTB, SGA
[4]	Coker et al (2016)	Los Angeles County, California, US	2000–2006	804 726	Case-control	Neighborhood-SES level	$PM_{2.5}$	TLBW
[5]	Darrow et al (2009)	Atlanta, US	1994–2004	476 489	Time-series	Race/ethnicity, maternal education	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, CO	PTB
[6]	Ebisu and Bell (2012)	Northeastern and mid-Atlantic US	2000–2007	1207 800	Case-control	Race/ethnicity	$PM_{2.5}$, PM_{10}	TLBW
[7]	Enders et al (2019)	California, US	2002–2013	2719 596	Case-control	Race/ethnicity, paternal education, neighborhood poverty rate	$PM_{2.5}$, PM coarse $(PM_{2.5-10})$	TLBW
[8]	Erickson et al (2016)	British Columbia, Canada	2001–2006	231,929	Case-control[a]	Neighborhood-level SES index, Asian immigrant density, urbanicity	$PM_{2.5}$	BW
[9]	Faiz et al (2013)	New Jersey, US	1998–2004	1719	Case-control	Race/ethnicity, maternal education, maternal age, smoking, prenatal care	$PM_{2.5}$, SO_2, NO_2, CO	Stillbirth
[10]	Faiz et al (2012)	New Jersey, US	1998–2004	756 562	Case-control	Race/ethnicity, maternal education	$PM_{2.5}$, SO_2, NO_2, CO	Stillbirth
[11]	Geer et al (2012)	Texas, US	1998–2004	1548 904	Case-control	Race/ethnicity	PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, O_3	BW
[12]	Green et al (2015)	California, US	1999–2009	3026 269	Case-control[a]	Race/ethnicity, maternal education	$PM_{2.5}$, SO_2, NO_2, CO	Stillbirth
[13]	Hao et al (2016)	Georgia, US	2002–2006	511 658	Case-control	Race/ethnicity, maternal education, area-level poverty level, urbanicity	$PM_{2.5}$, CO, NO_2	PTB
[14]	Laurent et al (2014)	Los Angeles County, California, US	2001–2008	960 945	Case-control	Race/ethnicity, maternal education, area-level income, hypertension, diabetes, preeclampsia	$PM_{2.5}$, $PM_{0.1}$, NO_2, O_3	TLBW
[15]	Le et al (2012)	Detroit, Michigan, US	1990–2001	164 905	Case-control	Race/ethnicity, maternal education	PM_{10}, NO_2, SO_2, O_3, CO	PTB, SGA
[16]	Lee et al (2013)	Allegheny County, Pennsylvania, US	1997–2002	34 705	Cohort	Race/ethnicity	$PM_{2.5}$, PM_{10}, O_3	PTB, SGA
[17]	Madsen et al (2010)	Norway	1989–2002	25 229	Case-control	Western ethnicity of mother	PM_{10}, $PM_{2.5}$, NO_2	BW, SGA

Table 1. (Continued.)

Study No.	Study	Location	Study period	Population size (No. births)	Study design	Effect modifiers	Air pollutant exposures	Health outcomes
[18]	Morelli *et al* (2016)	Grenoble and Lyon urban areas, France	2012	2790 000	Ecologic	European Deprivation Index (EDI)	$PM_{2.5}$	TLBW
[19]	Morello-Frosch *et al* (2010)	California, US	1996–2006	3545 177	Case-control	Race/ethnicity	$PM_{2.5}$, PM_{10}, PM coarse ($PM_{2.5-10}$), NO_2, SO_2, O_3, CO	BW
[20]	Ng *et al* (2017)	California, US	2002–2009	1050 330	Case-control[a]	Race/ethnicity, maternal education	$PM_{2.5}$	TLBW
[21]	Padula *et al* (2014)	California, US	2000–2006	263 204	Case-control	Race/ethnicity, neighborhood SES status, maternal education	$PM_{2.5}$, PM_{10}, CO, NO_2	PTB
[22]	Parker *et al* (2005)	California, US	2000	18 247	Case-control	Race/ethnicity, maternal education	$PM_{2.5}$, CO	BW, SGA
[23]	Pereira *et al* (2016)	Rochester, New York State, US	2004–2012	7121	Case-control	Race/ethnicity	$PM_{2.5}$	PTB
[24]	Pereira *et al* (2014b)	Connecticut, US	2000–2006	48 208	Cohort	Race/ethnicity	$PM_{2.5}$	PTB
[25]	Pereira *et al* (2014a)	Connecticut, US	2000–2006	271 204	Cohort	Race/ethnicity	$PM_{2.5}$	PTB
[26]	Ponce *et al* (2005)	California, US	1994–1996	59 700	Case-control	Neighborhood-level SES	Distance-weighted traffic density	PTB
[27]	Rappazzo *et al* (2014)	New Jersey, Ohio, and Pennsylvania in US	2000–2005	1940 213	Case-control[a]	Race/ethnicity	$PM_{2.5}$	PTB, VPTB
[28]	Ritz and Yu (1999)	Southern California, US	1989–1993	97 158	Case-control[a]	Race/ethnicity, maternal education	PM_{10}, CO, NO_2, O_3	PTB
[29]	Rudra *et al* (2011)	Western Washington State, US	1996–2006	3509 (mothers)	Cohort	Maternal employment	$PM_{2.5}$, CO	PTB
[30]	Salihu *et al* (2012b)	Florida, US	2000–2007	103 961	Case-control[a]	Race/ethnicity	$PM_{2.5}$, PM_{10}, PM coarse ($PM_{2.5-10}$)	TLBW, VLBW, PTB, VPTB, SGA
[31]	Salihu *et al* (2012a)	Hillsborough County, Florida, US	2000–2007	12 356	Case-control[a]	Race/ethnicity	$PM_{2.5}$, PM_{10}	TLBW, VLBW, PTB, VPTB, SGA
[32]	Schembari *et al* (2015)	Bradford City, England	2007–2010	9067	Cohort	Race/ethnicity	$PM_{2.5}$, PM_{10}, NOx, NO_2	BW
[33]	Schifano *et al* (2013)	Rome, Italy	2001–2010	234 945	Time-series	Race/ethnicity, maternal education, age, underlying clinical risk factors	PM_{10}, NO_2, O_3	PTB
[34]	Sheridan *et al* (2019)	California, US	2005–2010	2293 218	Cohort	Race/ethnicity	$PM_{2.5}$	PTB
[35]	Smith *et al* (2017)	Greater London, UK	2006–2010	540 365	Case-control	Infant's race/ethnicity	$PM_{2.5}$, NOx, NO_2	BW, TLBW, SGA
[36]	Stieb *et al* (2019)	Canada	1999–2008	1001 700	Cohort	Neighbor income	$PM_{2.5}$, NO_2, SO_2, CO, O_3	PTB
[37]	Stieb *et al* (2016)	Canada	1999–2008	2928 515			$PM_{2.5}$, NO_2	BW, TLBW, PTB, SGA

Table 1. (Continued.)

Study No.	Study	Location	Study period	Population size (No. births)	Study design	Effect modifiers	Air pollutant exposures	Health outcomes
					Case-control and cohort (2 different health datasets were used)	Maternal place of birth (within and outside Canada), area-level income		
[38]	Stieb *et al* (2015)	Canada	1999–2008	2966 705	Case-control	Maternal place of birth (within and outside Canada), area-level income	PM$_{2.5}$	TLBW, PTB, SGA
[39]	Tu *et al* (2016)	Atlanta, Georgia, US	2000	105 818	Case-control	Infant gender, area-level income	PM$_{2.5}$, O$_3$	BW, TLBW
[40]	Vinikoor-Imler *et al* (2014)	North Carolina, US	2003–2005	312 638	Case-control	Maternal education	PM$_{2.5}$, O$_3$	TLBW, SGA
[41]	Wang *et al* (2018)	30 provinces throughout mainland China	2013–2014	1300 342	Cohort	Maternal education, occupation, age, house-hold registration, pregnancy BMI, season of conception	PM$_1$	PTB
[42]	Winckelmans *et al* (2015)	Flanders, Belgium	1999–2009	525 635	Case-control	Maternal education, paternal education, infant sex, parity, maternal age, season	PM$_{10}$	BW, SGA
[43]	Wu *et al* (2009)	Los Angeles and Orange Counties, California, US	1997–2006	81 186	Case-control	Race/ethnicity, area-level poverty	PM$_{2.5}$, NOx, NO$_2$	PTB
[44]	Wu *et al* (2016)	California, US	2001–2008	4370 371	Nested case-control	Race/ethnicity, maternal education, body mass index, gestational weight gain	PM$_{2.5}$, NO$_2$, O$_3$	TLBW, PTB, pre-eclampsia, gestational diabetes mellitus
[45]	Yi *et al* (2010)	Seoul, South Korea	2000–2003	433 173	Case-control	Area-level household income	PM$_{10}$	PTB

[a] Notes. For the purposes of our systematic review, we refer to this study as a case-control study. The authors refer to the study as a cohort study. The study population was identified from a birth registry. We recognize that terms in epidemiology are not always used with perfect consistency; our goal is to use terms consistently within this review.

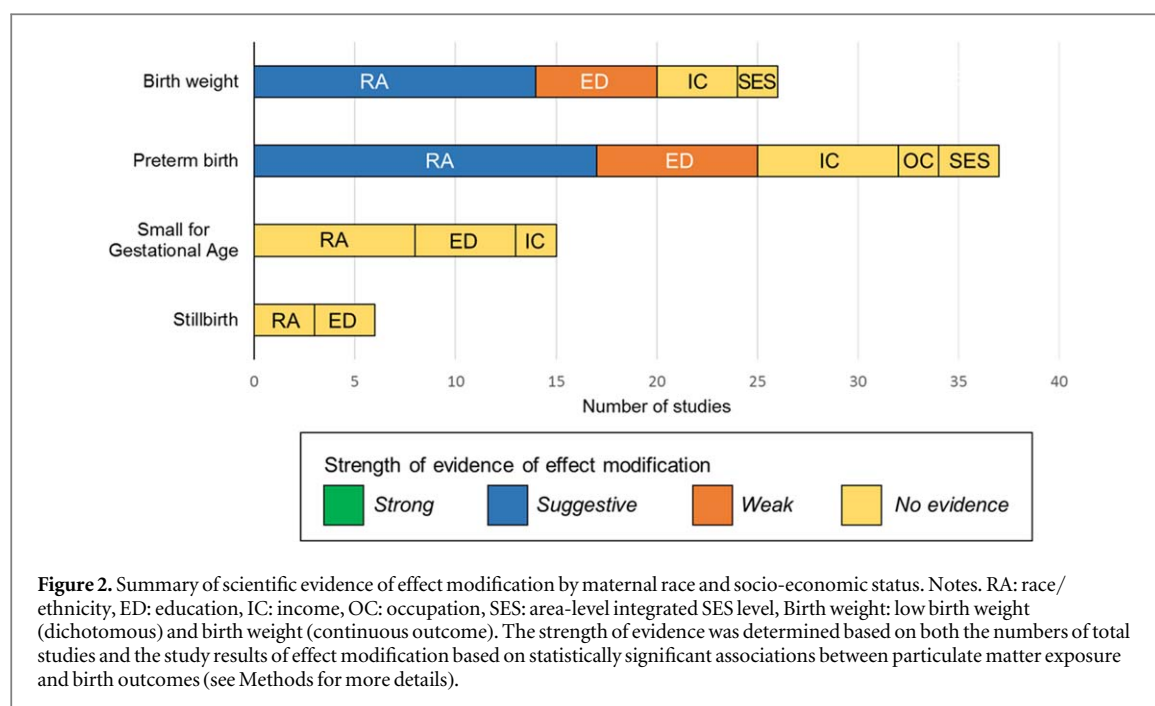The 'race/ethnicity' is maternal race/ethnicity, unless otherwise stated.

BW: Birth weight measured as continuous variable, TLBW: term low birth weight measured as dichotomous variable, SGA: small for gestational age, PTB: preterm birth, VPTB: very preterm birth, VLBW: very low birth weight measured as dichotomous variable.

Table 2. Summary of study characteristics of the identified 45 studies.

Criterion	Number of studies (%)	Study numbers (refer to table 1)
Research design		
Cohort	9 (20.0%)	16, 24, 25, 29, 32, 34, 36, 37, 41
Case-control	34 (75.6%)	1–4, 6, 7–15, 17, 19–23, 26–28, 30, 31, 35, 37–40, 42–45
Time-series	2 (4.4%)	5, 33
Ecologic	1 (2.2%)	18
Health outcomes[a]		
Birth weight (BW)(continuous)	12 (26.7%)	1, 2, 8, 11, 17, 19, 22, 32, 35, 37, 39, 42
TLBW (dichotomous)	15 (33.3%)	1, 4, 6, 7, 14, 18, 20, 30, 31, 35, 37–40, 44
Preterm birth	24 (53.3%)	3, 5, 13, 15, 16, 21, 23–31, 33, 34, 36–38, 41, 43–45
SGA	11 (24.4%)	3, 15–17, 22, 30, 31, 37, 38, 40, 42
Stillbirth	3 (6.7%)	9, 10, 12
Particulate matter exposure[a]		
PM$_{2.5}$	38 (84.4%)	1–14, 16–25, 27, 29–32, 34–40, 43, 44
PM$_{10}$	15 (33.3%)	2, 5, 6, 11, 15, 17, 19, 21, 28, 30–33, 42, 45
PM coarse (PM$_{10}$–PM$_{2.5}$)	3 (6.7%)	7, 19, 30
PM$_1$	1 (2.2%)	41
PM$_{0.1}$	1 (2.2%)	14
Exposure method		
Land use regression model	7 (15.6%)	4, 8, 29, 32, 37, 38, 42
Source receptor model	1 (2.2%)	20,
Interpolated estimates	5 (11.1%)	14, 16, 21, 34, 44
Fused model	2 (4.4%)	39, 41,
Dynamics models	8 (17.8%)	13, 17, 18, 27, 35, 40, 43, 44
Average within study area	6 (13.1%)	2, 5, 6, 11, 12, 36
Nearest monitor	14 (31.1%)	1, 3, 7, 9, 10, 19, 22–25, 28, 30, 31, 45
Single monitoring site	1 (2.2%)	17
Not specified	1 (2.2%)	33
Exposure period[a]		
Whole pregnancy	29 (64.4%)	1, 2, 4, 6, 7, 10, 11–14, 17, 19, 21–25, 30–32, 34, 35, 37, 38, 41–45
Each trimester	29 (64.4%)	1, 2, 6, 7, 10–16, 19–25, 32, 34, 35, 37, 38, 40–45
Others (e.g. annual average of study period, daily)	13 (28.9%)	3, 5, 9, 15, 26–29, 33, 36, 38, 39, 42
Not specified	2 (4.4%)	8, 18
Effect modifiers[a]		
Race/ethnicity of mothers	31 (68.9%)	1–3, 5–7, 9–17, 19–25, 27, 28, 30–34, 43, 44
Race/ethnicity of infants	1 (2.2%)	35
Educational attainment of mothers	17 (37.8%)	3, 5, 9, 10, 12–15, 20–22, 28, 33, 40–42, 44
Area-level household income or poverty level	9 (20.0%)	7, 13, 14, 36–39, 43, 45
Occupation of mothers	2 (4.4%)	29, 41
Area-level integrated SES	5 (11.1%)	4, 8, 18, 21, 26
Sensitivity analyses[a]		
Applying different sets of confounding variables in the health risk assessment	10 (22.2%)	2, 5, 7, 13, 14, 23, 24, 27, 30, 36
Changing distance of exposure assignment (i.e. buffer size)	7 (15.6%)	1, 10, 12, 19, 24, 30, 40
Excluding infants with certain conditions from the analyses (e.g. birth defects, exposure based on work address)	7 (15.6%)	7, 17, 21, 24, 32, 34, 35
Stratifying results by birth conditions (e.g. month of conception, cesarean section, parity, smoking status during pregnancy)	7 (15.6%)	2, 6, 15–17, 21, 24
Applying different air pollution data for the health risk assessment	3 (6.7%)	29, 37, 38

[a] Notes. Some studies may appear in more than one row.

TLBW = term low birth weight, SGA = small for gestational age.

Figure 2. Summary of scientific evidence of effect modification by maternal race and socio-economic status. Notes. RA: race/ethnicity, ED: education, IC: income, OC: occupation, SES: area-level integrated SES level, Birth weight: low birth weight (dichotomous) and birth weight (continuous outcome). The strength of evidence was determined based on both the numbers of total studies and the study results of effect modification based on statistically significant associations between particulate matter exposure and birth outcomes (see Methods for more details).

subgroups, were not significant, but the magnitude of the risks tended to be higher in African American/blacks. The other 3 studies showed no significant effect modification by race/ethnicity. Among 17 studies based on PTB and race/ethnicity, 5 studies found statistically significant risks of PM exposure, with estimated risks generally higher for African American/blacks, whereas 1 study showed significant and higher risk for infants of white mothers. Five other studies presented different magnitude of the risks by race/ethnicity but the risk estimates were not statistically significant so a clear evidence of effect modification was not present. Among those studies, 1 study conducted in Rome showed higher risks of preterm birth in infants of Italian mothers compared to others. While studies generally identified African American/blacks as the most vulnerable to PM-birth outcome associations for PTB and LBW, results were not consistent regarding which race/ethic group was the next most vulnerable. Among the 18 studies for PM-PTB association, the other 6 studies reported no significant evidence of effect modification of PTB by race/ethnicity. We concluded that there existed suggestive evidence that PM exposure risks for PTB and LBW are higher in infants of African-American/black mothers than in other racial/ethnical groups. Among 8 studies based on SGA and race/ethnicity, 2 studies reported significant and higher risks in African American/blacks, whereas 2 studies showed insignificant risk differences in the relationship between PM and SGA for racial/ethnical subpopulations and 4 studies found no evidence of effect modification by race/ethnicity. We concluded that there existed no current evidence of effect modification by race/ethnicity for SGA. No evidence was found for the effect modification by race/ethnicity for stillbirth, although our

conclusion is hindered by the small number of studies, while 1 study reported higher risks in white mothers for the relationship between PM and stillbirth with 2 other studies reporting no significant effect modification.

We identified studies comparing the relationship between PM exposure and birth outcomes by maternal educational attainment for PTB, LBW, SGA, and stillbirth. For PTB, 2 studies found that infants of mothers with less education had higher PM risk, whereas 6 studies did not find such evidence. Among 6 studies based on LBW, 2 studies reported significantly higher PM risks in infants of mothers with less education, 1 study reported significantly higher PM risks in mothers with higher education, and 3 studies reported no difference in the PM risk by maternal education level. Overall, weak evidence of higher PM risk for infants of mothers with less/high education existed for LBW and PTB. One study reported statistically significant results for the effect modification of PM risk for SGA by maternal education, whereas the 4 studies conducted in California did not find significant effect modification. We concluded that there was no evidence of higher risk of SGA from PM exposure in mothers with less education. The study results for stillbirth modified by maternal education were reported in 1 study showing a tendency of higher risk by lower education level but the results were not statistically significant (Hao *et al* 2016). Significant effect modification by maternal education was not found in the other 2 studies. Thus, we concluded that there existed no effect modification by maternal education on the relationship between PM exposure and stillbirth.

For effect modification by income, there were 7 studies for PTB, 4 studies for LBW, and 2 studies for SGA. No evidence was found for effect modification

by income for LBW and PTB as the studies reported no differences in PM risks by income level. We concluded that there is no evidence of effect modification was concluded for SGA, which may relate to the small number of studies.

One study examined the relationship between PTB and PM exposure as modified by mothers' occupation, reporting higher risks in infants of farmers than other workers. The other study did not find risk differences between mothers who were employed and those who were unemployed during pregnancy. We concluded no evidence of effect modification by occupation for the examined birth outcomes.

For the effect modification by area-level integrated SES levels, there were 2 studies for LBW and 3 studies for PTB. The 2 studies focusing on LBW reported significantly higher risks in regions with lower SES level. In the 3 studies for PTB, the differences in the association between PM exposure and PTB were not statistically significant or the risk differences were not based on statistically comparable risk measurements. In conclusion, there existed no evidence for effect modification by area-level integrated SES levels for PM risk of PTB and LBW.

4. Discussion

While a few previous meta-analyses and systematic reviews have investigated the association between maternal exposure to PM and adverse birth outcomes (Stieb *et al* 2012, Lamichhane *et al* 2015, Sun *et al* 2016, Li *et al* 2017), little is known about the vulnerability of birth outcomes to air pollution as modified by maternal risk factors. To our knowledge, this is the first study summarizing previously published study results to examine the evidence of different relationships between PM exposure and adverse birth outcomes by maternal risk factors.

We identified knowledge gaps in the evidence for effect modification of maternal race/ethnicity and SES factors. The most commonly examined effect modifier was race/ethnicity. This is likely due to a greater existence of information on race and ethnicity compared to information related to SES in most health data. We found suggestive evidence of effect modification by race/ethnicity for PM risk on PTB and birth weight but not SGA or stillbirth. Several mechanisms could explain health disparities by race/ethnicity. Biological differences in vulnerability to disease and mortality has been suggested as one factor contributing to the racial health disparities (Kawachi *et al* 2005). Exposure to PM can differ by race/ethnicity. Disproportionate exposure to air pollution among non-white versus white communities has been reported by numerous studies (Pratt *et al* 2015). For instance, a study using US census tract data showed that household-level $PM_{2.5}$ exposure was lower in neighborhoods with a larger white population across 6 US cities (Jones *et al*

2014). Race is also an indicator of fewer health-protective behaviors in the United States; whites were more likely to exercise and had more health care use than others, while African American/blacks and Hispanics were more likely to use tobacco and alcohol than whites (Dubay and Lebrun 2008). Race/ethnicity is associated, although not fully correlated with, socioeconomic status, which would affect health behaviors and health outcomes as well. Disparities in birth outcome risks among racial and ethnical groups may interplay with SES impacts. In the United States, various minority groups, particularly African American/ black communities, have been reported to be related to increased levels of a variety of environmental harms in relation to their economic and political vulnerabilities (Lester 2018). Health status such as death rates differs by racial/ethnical minority groups with higher risk in African American/black communities in the United States (Bell *et al* 2013). The summarized evidence of the disparities in the vulnerability of birth outcomes to PM by race/ethnicity in our review could be related to the SES factors that we reviewed (i.e. income, education), although their effects cannot be disentangled in our analysis. Diversity driven by immigration would put certain groups into more or less vulnerable conditions of the impact of air pollution on birth outcomes as well. A study suggested a weaker exposure-response relationship between PM and birth weight in populations with high density of Asian immigration (Erickson *et al* 2016), but generalization of the effect modification by immigration is yet unknown due to the small number of studies and genetic, diet, and other differences among Asian and other ethnicities.

We found that educational attainment was the second most studied effect modifier among the selected effect modifiers in our systematic review. Overall, the identified studies suggested that infants of mothers with lower education had higher risk of PTB and LBW associated with maternal exposure to PM, whereas we identified no significant effect modification for SGA or stillbirth. Maternal educational attainment is a known SES factor for vulnerability of birth outcomes associated with air pollution (Yi *et al* 2010). Different definition of educational attainment among studies and differences in educational systems across countries hinder integration of the effect modification results through quantitative risk combination (i.e. meta-analysis). Categorizations of maternal education level were relatively consistent for the US research among the identified studies and more than half of those studies focused on California (Laurent *et al* 2014, Padula *et al* 2014, Wu *et al* 2016, Ng *et al* 2017). Among them, 1 study conducted in Georgia had categories of less than high school (<9th), some high school (9–11th), completed high school (⩽12th), some college (<4 years), and completed college or more (⩾4 years) (Hao *et al* 2016), whereas the other 4 studies had categories of less than high school (<9th), high school

(9–12th), some college (<4 years), and completed college or more (≥4 years) (Laurent *et al* 2014, Padula *et al* 2014, Wu *et al* 2016, Ng *et al* 2017). Studies in China (Wang *et al* 2018) and Rome, Italy (Schifano *et al* 2013) categorized education level considering education lower than primary school as well as primary school. Some other studies (e.g. New Jersey, Europe, South Korea) had simpler categories such as high school or less (≤12 years) and more than high school (>12 years) (Yi *et al* 2010, Faiz *et al* 2013) or low, medium, and high education (Winckelmans *et al* 2015). Finer categorization of education level appears to be useful to examine if the risk in infants of mothers with mid-level (e.g. secondary) education is higher than the risk in infants of mothers with primary or tertiary education as previously observed by Wang *et al* (Wang *et al* 2018). Even though education categories are not completely consistent among studies, quantitative risk combination would become possible for simple categories of educational attainment (e.g. low versus high education) if more results based on finely resolved educational categories are reported from future studies.

Several studies examined effect modification using indices that combined information of multiple SES factors. The variables integrated into these SES indices were diverse and inconsistent among the identified studies and were measured at either the individual- or area-level. The variables included home ownership, marital status, occupational status, or education level for individual-level information, and median income, income from public assistance, employment rate, age of house, poverty level, or immigrant density for area-level information. Although independent comparison of effect modification by each of these variables or integration of the risk estimates for each variable are not viable among the studies, low level of integrated SES indices generally indicated higher effect estimates for the relationship between maternal exposure to PM and birth outcomes. Further assessments are required for effect modification by SES factors both independently and simultaneously considered with other correlated factors such as sex and race/ethnicity.

While SES factors should be adequately selected and interpreted in terms of plausible mechanisms (Andersen 2006), less attention has been paid to the consideration of more diverse SES variables that may affect the exposure to PM during the pregnancy other than education and income. For instance, job categories (e.g. white-collar versus blue-collar), occupation status and access to prenatal care may relate to general health of infants, but also to exposure patterns of air pollution. Furthermore, the importance of SES over life course as a determinant of health is increasingly recognized (Bell *et al* 2005). For infant health, birth outcomes can be determined by long-term adverse health behaviors like smoking or drug use, poor nutrition, inadequate health care, and stress of mothers (Hogan *et al* 2012). The SES indicators found in our review are common indicators used in health research of air pollution (Bell *et al* 2005). Nonetheless, these indicators do not capture the complex nature of the relationships among SES, exposure to air pollution, and birth outcomes because they define current state (e.g. current year income) but not historical status. Further efforts for understanding lifestyle, time-activity patterns, and exposure patterns of pregnant women through collecting rich maternal information from longitudinal cohort studies will be needed in research investigating environmental justice in relation to health risks of air pollution on birth outcomes.

Most of the 45 studies we reviewed used birth certificate data or birth registry data, while 7 studies utilized birth cohort data (Rudra *et al* 2011, Lee *et al* 2013, Basu *et al* 2014, Schembari *et al* 2015, Wang *et al* 2018, Sheridan *et al* 2019, Stieb *et al* 2019). Some studies using birth certificate data based on electronic databases (Coker *et al* 2016, Morelli *et al* 2016). One study used information at birth that was obtained from the official perinatal forms sent to the responsible non-profit association for perinatal data collection (Winckelmans *et al* 2015).

Health studies often rely on fixed-response categories of race/ethnicity from the health data source used, and the fixed-response may fail to explicitly represent complex self-identified race/ethnicity of individuals or communities in the study (Bradby 2003). Further, we found a discrepancy in the definition of race/ethnicity among the studies reporting effect modification by race/ethnicity. The terms 'non-Hispanic white' and 'non-Hispanic black' was used in 16 studies (Darrow *et al* 2009, Morello-Frosch *et al* 2010, Rudra *et al* 2011, Faiz *et al* 2012, Geer *et al* 2012, Salihu *et al* 2012a, 2012b, Faiz *et al* 2013, Basu *et al* 2014, Rappazzo *et al* 2014, Pereira *et al* 2014a, Green *et al* 2015, Benmarhnia *et al* 2017, Ng *et al* 2017, Enders *et al* 2019, Sheridan *et al* 2019). The terms 'white' or 'black' without specifying 'non-Hispanic' were used in 7 studies (Parker *et al* 2005, Bell *et al* 2007, Ebisu and Bell 2012, Le *et al* 2012, Pereira *et al* 2014b, Hao *et al* 2016, Smith *et al* 2017). The use of 'African American' distinguished from white (non-Hispanic) and Hispanic was found in 9 studies (Ritz and Yu 1999, Wu *et al* 2009, Ebisu and Bell 2012, Lee *et al* 2013, Laurent *et al* 2014, Padula *et al* 2014, Hao *et al* 2016, Pereira *et al* 2016, Wu *et al* 2016). For the Asian group, the term 'Asian' was the most used term in the reviewed studies (13 studies) (Ritz and Yu 1999, Parker *et al* 2005, Darrow *et al* 2009, Wu *et al* 2009, Rudra *et al* 2011, Laurent *et al* 2014, Padula *et al* 2014, Pereira *et al* 2014a, 2016, Hao *et al* 2016, Wu *et al* 2016, Smith *et al* 2017, Sheridan *et al* 2019), whereas 4 studies (Basu *et al* 2014, Green *et al* 2015, Ng *et al* 2017, Enders *et al* 2019) used the term 'Non-Hispanic Asian'. The uses of different categories and terminologies for race/ethnicity proposes a challenge for direct comparisons of the relationship between air pollution and adverse birth outcomes differed by race/ethnicity among

epidemiologic studies. Also, the use of broad categories that include many diverse subgroups can obscure differences that may be important for effect modification of air pollution's health impacts.

Exposure assessment has been conducted using several methods such as through linking individuals' residential addresses to local monitoring sites or from estimates based on advanced air pollution modeling. Air pollution modeling for individual-level exposure measurement can be divided into two methods: statistical models and dynamics model. Statistical models include land use regression, interpolation, and source-receptor models. Dynamics models include chemical transport, photochemical, and dispersion models. Some models combine multiple model types. The studies meeting our inclusion criteria used the following different methods to estimate exposure to PM: land use regression model, source receptor model, interpolation, fused model, dynamics model (dispersion model, chemical transport model), regional averaging of monitoring data, and use of data from the nearest monitor. A previous meta-analysis (Sun *et al* 2016) reported that the effect of $PM_{2.5}$ on LBW was higher and more significant when exposure to $PM_{2.5}$ was estimated based on dynamics models rather than observations at the nearest monitoring site from the participant's address or regional average of monitoring sites within a region. Another aspect of the methods that varied among studies was residential mobility, as women can move during pregnancy, yet many studies assess exposure during pregnancy based on the residence at time of delivery, which can introduce exposure misclassification (Bell and Belanger 2012, Bell *et al* 2018, Tang *et al* 2018). Due to the small number of the total studies and wide range of methods included in our study, we did not compare effect modification based on PM associations assessed using different exposure methods, which warrants further study. As exposure methods can differentially affect exposure estimates and their uncertainty by population demographics (Butland *et al* 2013, Ebisu *et al* 2014), research on this issue is needed for different regions and subpopulations.

Although partner's risk factors (e.g. occupation status, education, income, smoking status) likely affect general living quality of the family and the infants, partner's information was far less considered in the identified studies. Studies have mostly relied on availability of mother's information, marital status, and community-level SES variables as surrogates for related information. We found that 4 studies among the 45 identified studies considered partner's information for assessing the impact of PM on birth outcomes such as smoking or race/ethnicity (Bell *et al* 2007, Winckelmans *et al* 2015, Wang *et al* 2018, Enders *et al* 2019). In many cases, such variables may not be available in the underlying health data used by the studies.

In our review, we found that the number of studies addressing effect modification by maternal race/ethnicity and SES factors was smaller for SGA and stillbirth compared to LBW or PTB. Despite the evidence of the racial/ethnical disparity of stillbirth trends in the U.S. population and etiological studies for causes of stillbirth (Salihu *et al* 2004), there still exists a lack of studies for racial/ethnical disparity for the relationship between air pollution and stillbirth that could provide important information for improvement of global and local maternal and fetal health. The paucity of studies for stillbirth might be related to the complexity of identifying cases of stillbirth in populations. Data collection for stillbirths is often executed utilizing death certificate data and population-based birth defects surveillance programs (Duke *et al* 2009, Basu *et al* 2016). The different terms describing the death of the fetus include miscarriage, spontaneous abortion, and stillbirth, relating to different time points during pregnancy (Munoz *et al* 2016). Furthermore, the methods of diagnosis and terminologies for stillbirth can vary across different countries and among the states within a country (Munoz *et al* 2016) although several guidelines for diagnosis and data collections for fetus deaths have been provided (Pathirana *et al* 2016, Alexander and Zeitlin 2017). The complexity of the definition of stillbirth would challenge accurate detection of stillbirth in populations and comparison of risk trends among epidemiologic studies regarding the different impacts of air pollution on birth outcomes by race/ethnicity and SES. However, our reviewed studies did not provide opportunities for examining the different definitions of stillbirth due to the small study number; thus, this remains an area of needed research.

Limitations of our study include the small number of relevant studies and geographically limited estimates for effect modification of the relationship between air pollution exposure and birth outcomes. Due to the small number of studies, it was not feasible to conduct a quantitative risk summarization; instead we provide a narrative summary of the evidence of effect modification based on the identified studies and our study should be interpreted in this context. Still our study captures and describes the existing literature on this topic.

A strength of this study is that we critically highlight research gaps for the evidence of effect modification by various maternal risk factors covering race/ethnicity and SES. The differences in the PM-adverse birth outcome relationships among subpopulations found in our review imply environmental injustice and provide important information relevant to decision-making for identifying and protecting vulnerable subpopulation.

5. Conclusion

This systematic review on epidemiologic studies was conducted to understand how the associations

between PM exposure and adverse birth outcomes differ by maternal demographic and socio-economic factors. Our review identified higher and more statistically significant magnitude of effect estimates for PM exposure and risk of LBW and PTB for infants of mothers who were African American/black or had lower educational attainment. Epidemiologic studies addressing disparities in the risk of PM by maternal SES have been disproportionately conducted for some types of birth outcomes with more attention on PTB and LBW. Evidence of effect modifications was not clearly present for income, occupation, and area-level SES in the reviewed studies, although our conclusions are limited by the small study numbers, whereas a larger volume of evidence existed for maternal race/ethnicity and educational attainment. Moreover, we found that only limited types of socio-economic factors were examined in previous studies. As a result, we suggest that more studies are required to understand potential effect modification of the risk of SGA and stillbirth due to maternal exposure to PM during pregnancy. Future studies are also needed for other socio-economic factors that can potentially play a role as effect modifiers such as income, job categories, occupation status, and access to prenatal care. Lastly, additional efforts to understand the interplay of race/ethnicity and SES on vulnerability of birth outcomes to air pollution are needed to provide information for identifying vulnerable communities and populations and planning preventive measures.

Acknowledgments

Appendix

To summarize study designs that were used in the identified eligible studies, we set our criteria to use terms consistently within this review. Epidemiologic studies on birth outcomes often utilize pre-existing health data such as birth registry or birth certificate data and some authors refer to their study as a retrospective cohort study. However, we categorized this method as case-control study design as those studies identified the case and control groups using birth registry data before they assigned the exposure

level to each birth. In other words, this method did not enroll a cohort and follow the population, or choose a cohort based on the exposure status before the outcome status occurs for the cohort. We recognize that the names of epidemiologic study designs can be used in different ways in the literature; our goal here is to use them consistently within this review. We categorized a study as a cohort study only when study participants were followed for the period of pregnancy before the delivery. In table 1, we marked studies that authors referred to as a cohort study but that we identified as a case-control design based on our criteria in this review. For example, Green *et al* referred to their study as a cohort study (Green *et al* 2015) but we referred to the study as a case-control study in this review based on the following reasons; the study population was based on all live births and stillbirths obtained from the birth data by the California Office of Vital Statistics and PM$_{2.5}$ exposure level during the pregnancy was assigned to each stillbirth or non-stillbirth infant. Our criteria and results on the summarized study designs do not imply that epidemiologic studies have been used inaccurate terms. It shows that terms for study designs are not always used with perfect consistency for studying the relationship between air pollution and birth outcomes.

Data availability statement

Any data that support the findings of this study are included within the article. The reviewed articles are listed in the main text and the reference list. The findings of those reviewed articles are detailed in online supplementary material.

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