

# Ambient and household air pollution on early-life determinants of stunting – a systematic review and meta-analysis

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## Research article

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## Abstract

**Background** Stunting is an important risk factor for early growth and development with health implications throughout the life course. While maternal exposure to particulate matter (PM) has been linked to early determinants of stunting, existing evidence has rarely captured the most vulnerable populations.

**Methods** We conducted a systematic review and meta-analysis of the peer-reviewed literature to assess the evidence of the association between ambient and household PM pollution exposure and postnatal stunting (height-for-age z-score), and prenatal determinants (i.e., intrauterine growth restriction and small for gestational age) that would greatly increase children's risk of stunting. Relevant manuscripts published from 2000 to 2019 were reviewed. Random effect models were used to estimate pooled odds ratios (OR).

**Results** Thirty-two studies conducted in 18 countries met our inclusion criteria. We found significant positive associations between prenatal determinants of stunting and a 10  $\mu\text{g}/\text{m}^3$  increase in PM 2.5 during the first trimester (OR=1.02; 95% confidence interval (CI): 1.00–1.04) and second trimester (OR=1.04; 95% CI, 1.01–1.07). Similar associations were found for prenatal determinants of stunting of high versus low quartiles of PM 2.5 exposure during the whole pregnancy. Postnatal stunting was found to be positively, though insignificantly, associated with postnatal exposure to household air pollution.

**Conclusions** Our analysis shows evidence of increased risk of prenatal determinants of stunting with ambient particulate exposure, especially during first trimester, and suggestive evidence of elevated stunting risk with postnatal exposure to household air pollution. This evidence reinforces the importance of promoting clean air as part of an integrated approach to preventing stunting.

## Background

Air pollution is a major environment-related health threat and an important determinant of child health globally. The World Health Organization (WHO) recognizes air pollution as “an overlooked health emergency for children around the world,” noting that the issue can be especially severe for children living in low- or middle-income countries [1]. In 2017, air pollution exposure was responsible for nearly 372,000 deaths in children under 5, making it the third leading risk factor for premature death after malnutrition and unclean water [2]. Unlike many more prominent risk factors, air pollution is pervasive. WHO (2018) estimates that 93% of children and teens  $\leq 15$  years globally are exposed to ambient air pollution levels higher than 10  $\mu\text{g}/\text{m}^3$ , the health-based limit in WHO's Air Quality Guidelines. Burning or fuel combustion is the main source of air pollutants most harmful to human health, the most important being particulate matter less than 2.5 microns in diameter (PM<sub>2.5</sub>). PM<sub>2.5</sub> at high concentrations can manifest as smoke or haze, but it causes health effects at concentrations even too low to be visible. Exposure to elevated levels of particulate matter during childhood is associated with increases in pneumonia, asthma, bronchitis and other respiratory infections and diseases [3, 4]. In recent years, many researchers have turned to elucidating the relationship between in utero exposures and adverse pregnancy outcomes, such as low birthweight and preterm delivery.

Stunting, or linear growth failure in childhood, is a largely irreversible outcome with long-term impacts on children and their communities. In addition to height and physical development concerns, stunted children often achieve lower developmental test scores and suffer from diminished cognitive development and reduced economic activity [4–9]. Stunting begins in utero, and manifests mostly during the first two years of postnatal life, with increasing prevalence until age 5 [10–12]. Globally, an estimated 149 million (22%) children under 5 in 2018 were stunted, with a height-for-age z score (HAZ) of  $-2$  standard deviations (SD) below the WHO child growth standards median [8]. The highest prevalence of stunting is in Oceania (38%), followed by Southern Asia (33%) and Southeast Asia (25%) [8].

## Study Purpose and Rationale

Two previous meta-analyses have suggested positive associations between ambient PM<sub>2.5</sub> pollution and adverse pregnancy outcomes, defined as small for gestational age (SGA) or intrauterine growth retardation (IUGR) [13], and between household air pollution from cooking using solid fuels and postnatal stunting measured by HAZ [14]. However, considerable gaps in the evidence remain, especially regarding the strength of evidence for household air pollution or ambient pollution concentrations several-fold greater than the WHO air quality guidelines, both of which occur in regions with the highest stunting prevalence. We therefore aimed to provide an up-to-date systematic review and meta-analysis of the evidence of association of ambient and household air pollution on stunting-related outcomes. Specifically, we reviewed all studies that examined adverse pregnancy outcomes (i.e. SGA, IUGR) that also serve as prenatal determinants of stunting. Based on a meta-analysis of 19 longitudinal birth cohorts, Christian et al. [15] found that SGA was associated with 2.4 times the odds of postnatal stunting in low- and middle-income countries, and a recent study using a birth cohort in the United States even reported a 3.55 odds of stunting among SGA newborns at age 5 years as compared to newborns appropriate for gestational age [16]. In addition, we included studies that evaluate the impact of air pollution on postnatal stunting (i.e., HAZ) among children aged 0–59 months.

## Methods

### Search Strategy

A systematic search of peer-reviewed articles that assessed the effect of ambient and household particulate matter exposure during or post-pregnancy on stunting-related outcomes was carried out on PubMed and Google Scholar in May 2019. The following terms were used in the search: “air pollution” or “particulate matter” or “indoor air pollution” or “household air pollution” or “solid fuel” or “biomass” AND “adverse pregnancy outcomes” or “adverse birth outcomes” or “stunting” or “height-for-age” or “HAZ” or “small for gestational age” or “SGA” or “intrauterine growth retardation” or “IUGR”. All original studies published between January 2000 and April 2019 were considered. Reference lists of previous relevant published reviews, meta-analyses, and the identified articles were also searched. The last search was updated on 17 May 2019. Daily time-series studies, case reports, case studies and studies available only in

abstract form were excluded. All studies were evaluated independently by two reviewers to ensure identified articles were suitable for inclusion in the meta-analysis. Reporting of findings of this systematic review also complies with the PRISMA statement [17].

## Eligibility Criteria and Study Selection

Eligible studies included in the meta-analysis met all the following inclusion criteria: (1) original articles examining exposure to particulate matter with aerodynamic diameter less than 10  $\mu\text{m}$  ( $\text{PM}_{10}$ ),  $\text{PM}_{2.5}$ , or household air pollution exposure from cooking with solid fuel; (2) definitions of growth faltering: moderate and severe stunting defined as  $\text{HAZ} < -2$  SD, and severe stunting defined as  $\text{HAZ} < -3$  SD of the WHO child growth standards or reference population median; SGA defined as birth weight below the 10th percentile for a given gestational age and gender of the newborn in the study population or similar; or IUGR defined as birth weight below the 10th percentile for gestational age or similar; (3) quantitative evaluation (i.e. linear or logistic regression coefficients) of the relationship; (4) exposure period was calculated as whole pregnancy and/or specific trimesters; (5) articles were written in English. Studies or effect estimates were excluded if one or more of the following occurred: (a) did not meet at least one of the above inclusion criteria; (b) exposure period (e.g. trimester-specific, during or post pregnancy) was not explicitly reported; (c) effect estimates in studies could not be converted into odds ratio (OR) and 95% confidence intervals (CI) in risk of stunting; (d) studies adjusted for two or more pollutants in the same model; (e) reviews and repeat literature including secondary analysis of data. For multiple publications of the same birth population in a region of the same outcome, only the study with the largest number of observations and/or the longest study period was included in the meta-analysis to avoid the overlapping datasets in the same outcome. Likewise, if multiple estimates using various exposure assessment tools (e.g. monitoring, satellite) of the same outcome from the same population were presented in a single study, only estimates with the largest sample size and/or smallest standard errors were included.

## Data extraction and statistical analysis

Information extracted from each study included: first author's surname, year of publication, country, study period, birth population, birth outcomes, exposure type (e.g.  $\text{PM}_{2.5}$ , solid fuel), exposure assessment (e.g. satellite, monitoring data), exposure period (e.g. trimester-specific and/or entire pregnancy), risk measure (e.g. odds ratio, relative risk), effect size, and adjustment of other factors or covariates. As all eligible studies that examined ambient particulate pollution reported effect estimates either for continuous exposure (when they assumed linear associations) or by categories (e.g. tertiles, quartiles, or quintiles) of exposure, we performed all analyses using both continuous exposure (per 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  or  $\text{PM}_{10}$  concentration) and categorical exposure defined as high vs. low, where the high level was defined as the highest study-specific category and the low level as the lowest study-specific category. For household particulate pollution, all analysis was performed using categorical exposure defined as high vs low exposure. To ensure comparability, reported relative risks were converted to ORs using the approximation approach described by Zhang and Yu [18] if information on cases and non-cases were available from the study.

Given that SGA and IUGR are often used interchangeably, both outcomes were analyzed together as SGA in our study. A random effects model was used to estimate the pooled effect measures, with between-study heterogeneity assessed using  $I^2$  statistic (25%, 50%, and 75% were used as rules of thumb for low, moderate and high heterogeneity, respectively) [19]. In this meta-analysis, effect estimates were grouped by exposure period (e.g. trimester-specific), and heterogeneities were also analyzed by exposure period. The possible publication bias was assessed with a Begg's test and the degree of asymmetry was evaluated by Egger's tests [20, 21]. As part of the sensitivity analysis, each eligible study was removed one-by-one from the meta-analysis to examine the robustness of our pooled ORs. We restricted the analysis to eligible studies that had the same outcome definitions. All statistical analyses were performed using R Software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria), and a p-value < 0.05 is considered statistically significant.

## Results

### Characteristics of included studies

Of the 210 articles identified in the literature search and reference lists of previous relevant reviews, meta-analyses, and identified articles, 57 articles with possibly eligible titles were selected by either reviewer, and 11 were subsequently excluded because the abstracts were irrelevant. Full manuscripts of the remaining 46 articles (37 on ambient, nine on household) were reviewed. Of 37 studies that examined ambient particulate pollution, 28 were restricted to either SGA or IUGR and ambient  $\text{PM}_{2.5}$  or  $\text{PM}_{10}$  pollution exposure during the entire pregnancy, and/or any of the three trimesters. Nine studies were not considered further due to the small number of effect estimates for a meta-analysis, and these studies fell into three categories: they either 1) evaluated very small for gestational age [22], HAZ [23], or physician-diagnosed fetal growth restriction [24] as outcome measures; 2) examined total suspended particles [25], particles with aerodynamic diameter of 7 microns or less [26], or  $\text{PM}_{10}$  emitted from incinerators [27] as exposure measure; or 3) evaluated exposure during first month of pregnancy [28] or post pregnancy [29, 30]. Of nine studies that evaluated household air pollution, six examined the impact of post-pregnancy exposure on HAZ as a dichotomous measure, whereas one employed HAZ as a continuous measure [31], and another compared stunting risk from pollution from indoor cooking with that from outdoor cooking [32]. Additional information was not available from four studies to allow the conversion from relative risks to OR. Therefore, we included in the final meta-analyses 26 articles on ambient air pollution and five articles on household air pollution, stratified by outcome, exposure measure and gestational age. Figure 1 shows the study screening process.

Table 1 summarizes the characteristics of the studies included in this review. Of 26 studies on ambient air pollution, most were from countries with low ambient air pollution concentrations (e.g. the United States). Three studies were from Asia and one was from Australia. Study periods ranged from 1975 to 2017, with the majority of the individual studies conducted in the 2000s. The population of participants from individual studies ranged from 1,514 to 3 million. Exposure assessment methods of most studies were based on existing central monitoring data, while a few used advanced monitoring approaches (e.g. satellite data, or modeled pollution measurement from land-use regression models).  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  exposures ranged from 4 to 71  $\mu\text{g}/\text{m}^3$  and from 12 to 102  $\mu\text{g}/\text{m}^3$ , respectively.

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

First Author	Year Published	Country	Data Year	Study design	Sample Size	% of outcome	Exposure Measure	Exposure Period	Outcome	SES adjusted?
Wang et al. 2019	2019	Guangzhou, China	2015–2017	Retrospective cohort study	506,000	9.7%	PM 2.5, PM 10	Entire pregnancy, trimesters	SGA	No
Percy et al. 2019	2019	Ohio, USA	2007–2010	Retrospective cohort study	224,921	10.8%	PM 2.5	Entire pregnancy, trimesters	SGA	No
Smith et al. 2017	2017	London	2006–2010	Retrospective cohort study	540,365	9.5%	PM 2.5, PM 10	Entire pregnancy	SGA	Yes
Lavigne et al. 2016	2016	Canada	2005–2012	Retrospective cohort study	818,400	9.3%	PM 2.5	Entire pregnancy, trimesters	SGA	Yes
Stieb et al. 2016	2016	Canada	1999–2008	Retrospective cohort study	2,966,705	8.3%	PM 2.5	Entire pregnancy, trimesters	SGA	No
Pereira et al. 2016	2016	Connecticut, USA	1988–2008	Retrospective cohort study	9,587	na	PM 10	Entire pregnancy, trimesters	SGA	No
Qian et al. 2016	2016	Wuhan, China	2010–2013	Prospective cohort study/case-control study	95,911	8.8%	PM 2.5, PM 10	Entire pregnancy, trimester 1	IUGR	Yes
Capobussi et al. 2016	2016	Italy, Europe	2005–2012	Retrospective cohort study	27,128	10.2%	PM 10	Entire pregnancy, trimesters	SGA	Yes
Winckelmans et al. 2015	2015	Belgium	1999–2009	Retrospective cohort study	494,653	9.4%	PM 10	Entire pregnancy, trimesters	SGA	No
Hannam et al. 2014	2014	UK	2004–2008	Retrospective cohort study	5,721	8.6%	PM 2.5, PM 10	Entire pregnancy	SGA	Yes
Hyder et al. 2014	2014	Connecticut and Massachusetts, USA	2000–2006	Retrospective cohort study	643,839	10.0%	PM 2.5	Entire pregnancy, trimesters	SGA	No
Gray et al. 2014	2014	North Carolina, USA	2002–2006	Retrospective cohort study	457,642	9.3%	PM 2.5	Entire pregnancy	SGA	No
Lee et al. 2013	2013	Pennsylvania, USA	1997–2002	Retrospective cohort study	34,705	8.5%	PM 2.5, PM 10	Trimester 1	SGA	No
Sathyanarayana et al. 2013	2013	USA	1997–2005	Retrospective cohort study	298,835	10.2%	PM 2.5	Trimesters	SGA	Yes
Salihu, et al. 2012	2012	USA	2000–2007	Retrospective cohort study	12,356	12.9%	PM 2.5, PM 10	Entire pregnancy	SGA	No
van den Hooven, et al. 2012	2012	Netherlands	2001–2006	Prospective cohort study	6,997	5.5%	PM 10	Entire pregnancy	SGA	No
Le, et al. 2012	2012	Michigan, USA	1990–2001	Retrospective cohort study	24,096	8.3%	PM 10	Trimesters	SGA	No
Madsen, et al. 2010	2010	Norway	1999–2002	Retrospective cohort study	25,229	9.6%	PM 2.5, PM 10	Entire pregnancy	SGA	No
Rich, et al. 2009	2009	New Jersey, USA	1999–2003	Retrospective cohort study	88,678	8.2%; 2.4%	PM 2.5	Trimesters	SGA; VSGA	Yes
Brauer, et al. 2008	2008	Canada	1999–2002	Retrospective cohort study	70,249	9.0%	PM 2.5, PM 10	Entire pregnancy	SGA	Yes
Liu, et al. 2007	2007	Canada	1985–2000	Retrospective cohort study	386,202	10.9%	PM 2.5	Trimesters	IUGR	No
Hansen, et al. 2007	2007	Australia	2000–2003	Retrospective cohort study	26,617	7.1%	PM 10	Trimesters	SGA	Yes
Kim, et al. 2007	2007	Seoul, Korea	2001–2004	Prospective cohort study	1,514	0.9%	PM 10	Trimesters	IUGR	No

First Author	Year Published	Country	Data Year	Study design	Sample Size	% of outcome	Exposure Measure	Exposure Period	Outcome	SES adjusted?
Parker, et al. 2005	2005	California, USA	2000	Retrospective cohort study	18,247	8.4%	PM 2.5	Entire pregnancy	SGA	No
Mannes, et al. 2005	2005	Australia	1998–2000	Retrospective cohort study	138,056	9.7%	PM 2.5, PM 10	Trimesters	SGA	Yes
Salam, et al. 2005	2005	California, USA	1975–1987	Retrospective cohort study	3,901	15.0%	PM 10	Entire pregnancy, trimesters	IUGR	Yes
Kim, et al. 2017	2017	South Asia (pooled)	2005–2014	Cross-sectional study	18,586	38.4%	Use of solid fuel	Post-pregnancy (6–23 months)	HAZ	Yes
Machisa, et al. 2013	2013	Swaziland	2006–2007	Cross-sectional study	1,150	27.6%	Use of biomass fuel	Post-pregnancy (6–36 months)	HAZ	Yes
Tielsch, et al. 2009	2009	India	1998–2000	Prospective cohort study	10,437	89.4%; 57.5%	Use of wood/dung fuel	Post-pregnancy (0–6 months)	HAZ; SGA	No
Kyu, et al. 2009	2009	Cambodia, DR, Haiti, Jordan, Moldova, Namibia, Nepal	2005–2007	Cross-sectional study	28,439	14.8%; 8%	Exposure to biofuel smoke	Post-pregnancy (0–59 months)	HAZ	Yes
Fenske, et al. 2013	2013	India	2005–2006	Cross-sectional study	12,176	36.8%; 17.1%	Use of diff cooking fuels	Post-pregnancy (0–24 months)	HAZ	No

Conversely, most studies on household air pollution included in the meta-analysis were from areas where a high proportion of the population uses solid fuels: Asia ( $n = 4$ ), followed by South America ( $n = 1$ ) and Africa ( $n = 1$ ). One study contained data from seven developing countries across the globe [33]. The number of participants from individual studies ranged from 202 to nearly 28,500, and the average percentage of population using solid fuels in countries from those studies was 62% (range from 21–91%). Overall, covariate adjustments varied considerably though key adjustments included maternal age, maternal education, parity and infant sex. Thirteen studies adjusted for socioeconomic status and 19 studies adjusted for tobacco use.

## Pooled estimates of ambient air pollution

A summary of the results from adverse pregnancy outcomes is shown in Table 2. Figure 2 shows forest plots of the pooled OR estimates for SGA with a  $10 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  based on the whole pregnancy period and/or one of the three gestational periods (the first, second, or third trimesters). The estimates are sorted by the mean exposure levels reported. The pooled ORs indicated significant positive associations between SGA and a  $10 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  during the first (OR = 1.02; 95% CI: 1.00–1.04) and second trimesters (OR = 1.04; 95% CI: 1.01–1.07). Elevated pooled odds ratios were also observed for the whole pregnancy period (OR = 1.04; 95% CI: 1.00–1.10) and third trimester (OR = 1.02; 95% CI: 0.98–1.07), though the associations were not statistically significant at the alpha level of 0.05. A similar pattern of association was observed for stunting risks of high versus low quartiles of  $\text{PM}_{2.5}$  exposure during the whole pregnancy (Table 2). Likewise, significant elevated odds of SGA associated with a  $10 \mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$  for the first trimester (OR = 1.03; 95% CI: 1.00–1.06) was observed (S1 Figure), as well as risk associated with high versus low quartile of  $\text{PM}_{10}$  exposure during the whole pregnancy (OR = 1.10; 95% CI: 1.02–1.18).

Table 2  
Summary of combined effect estimates on stunting associated with particulate exposures

Outcome and PM type	Exposure measure	Trimester	No. of studies	Test of associations (random effect)		Test of heterogeneity		Publication bias	
				OR [95% CI]	p-value	$I^2$ (%)	p-value	Begg's test (p-value)	Egger's test (p-value)
Ambient air pollution									
SGA and PM <sub>2.5</sub>	Continuous (per 10 µg/m <sup>3</sup> )	Entire pregnancy	10	1.044 [0.986, 1.104]	0.1372	92%	< 0.0001	0.3252	0.4056
		Trimester 1	9	<b>1.023 [1.003, 1.045]</b>	<b>0.0258</b>	81%	< 0.0001	0.9999	0.1883
		Trimester 2	8	<b>1.041 [1.011, 1.072]</b>	<b>0.0064</b>	80%	< 0.0001	0.9999	0.7292
		Trimester 3	8	1.025 [0.980, 1.073]	0.2797	90%	< 0.0001	0.6207	0.2550
	Categorical (high vs low)	Entire pregnancy	4	1.048 [0.982, 1.119]	0.1565	0.0%	0.7702	0.4969	0.6590
SGA and PM <sub>10</sub>	Continuous (per 10 µg/m <sup>3</sup> )	Entire pregnancy	7	1.041 [0.993, 1.092]	0.0961	87%	< 0.0001	0.0985	0.2984
		Trimester 1	8	<b>1.029 [1.001, 1.058]</b>	<b>0.0433</b>	77%	< 0.0001	0.4579	0.4007
		Trimester 2	7	1.029 [0.987, 1.072]	0.1770	80%	< 0.0001	0.2931	0.8763
		Trimester 3	6	1.012 [0.981, 1.044]	0.4582	60%	< 0.0001	0.5730	0.3575
	Categorical (high vs low)	Entire pregnancy	5	<b>1.097 [1.018, 1.181]</b>	<b>0.0146</b>	35%	0.1854	0.2672	0.3272
Household air pollution									
HAZ < - 2SD*	Use of solid fuel (high vs. low)	Post pregnancy	5	1.129 [0.969, 1.314]	0.1202	63%	0.0297	0.9999	0.8769
HAZ < - 3SD		Post pregnancy	3	1.123 [0.996, 1.265]	0.0548	18%	0.2953	0.6015	0.3265

\* SD refers to standard deviation. Bold font indicates statistical significance at alpha = 0.05 level.

Overall, the heterogeneities of all studies were estimated in random-effect models. We observed a high degree of heterogeneity ( $I^2 \geq 60\%$ ) among studies that used continuous measure of PM<sub>2.5</sub> and PM<sub>10</sub> as exposure metric (e.g. SGA and PM<sub>2.5</sub> for entire pregnancy,  $I^2 = 92\%$ ,  $p < 0.001$ ), but not for studies that reported findings for categorical measures of PM<sub>2.5</sub> and PM<sub>10</sub> (PM<sub>2.5</sub>,  $I^2 = 0\%$ ,  $p = 0.77$ ; PM<sub>10</sub>,  $I^2 = 51\%$ ,  $p = 0.10$ ). Our pooled estimates were robust; removing a particular study did not affect the pooled estimates by > 5%, though the significance of the associations may change in some instances (**S3 Figure**). For SGA and PM<sub>2.5</sub> (continuous) exposure during the first trimester, when either Hyder et al. (2014), Liu et al. (2007), Rich et al. (2009) or Qian et al. (2016) was removed, the observed association was no longer formally statistically significant. Similarly, removing the study by Lavigne et al. (2016) also results in insignificant stunting risk. Nonetheless, there was no significant publication bias for both exposures and outcomes according to both Begg's and Egger's tests ( $p > 0.05$ ).

## Pooled estimates of household air pollution

Two pooled estimates associated with household exposure to solid fuels during the entire pregnancy were calculated for both moderate and severe (defined by HAZ < - 2 SD) and severe (HAZ < - 3 SD) stunting (Fig. 3). Pooled OR for moderate and severe stunting from five epidemiologic studies is 1.13 (95% CI: 0.97–1.31; Table 2), with moderate heterogeneity ( $I^2 = 63\%$ ;  $p = 0.03$ ) and no publication bias ( $p > 0.05$  for both Begg's and Egger's tests). For severe stunting only, there was no evidence of statistical heterogeneity ( $I^2 = 18\%$ ;  $p = 0.2953$ ) nor publication bias, and the pooled estimate is 1.12 (95% CI: 1.00–1.27; **S2 Figure**). Sensitivity analysis showed that removing the study by Kim et al. (2017) results in a statistically significant increase in odds of moderate and severe stunting (**S4 Figure**).

## Discussion

In this comprehensive quantitative analysis, we summarized the most up-to-date evidence of the associations between prenatal and postnatal exposure to ambient and household air pollution on SGA, IUGR and HAZ from 31 epidemiologic studies published on or before May 2019. The pooled effect estimates consistently suggest a moderate, but noteworthy increase in the risk of SGA (including IUGR). A 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> during the first trimester was associated with a 2.3% increase (95% CI: 0.03–4.5%) in risk of SGA, and between a 2% and 11% elevated risk is observed with increased exposure to PM

during various gestational exposure periods, including the first and second trimesters (PM<sub>2.5</sub>) and over the entire pregnancy (PM<sub>10</sub>). The direction of the associations between household air pollution and moderate and severe stunting (defined as HAZ < - 2 SD) are consistent with that for ambient air pollution and SGA, though the associations are not statistically significant.

We identified three previous systematic reviews linking air pollution and SGA, IUGR, and HAZ [13, 14, 38]. Two reviews focused on the impact of ambient PM<sub>2.5</sub> exposure on various adverse pregnancy outcomes that included SGA. Only one review provided pooled effect estimates [13], while the other offered qualitative observations of the evidence [38]. In a 2015 review, Zhu et al. [13] reported ORs of 1.07 (95% CI: 1.05–1.10) and 1.06 (95% CI: 1.02–1.10) for SGA per increase in PM<sub>2.5</sub> exposure during first and second trimesters, as well as statistically significant associations for the third trimester and the entire pregnancy. Our pooled OR estimates of 1.02 and 1.04 for SGA per 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> during the first and second trimesters, respectively, are slightly smaller in magnitude than those from previous meta-analyses. One explanation for this discrepancy is that individual epidemiologic studies that were published after the 2015 meta-analysis tend to report effect estimates that are lower in magnitude and statistical significance as compared to those from earlier studies. Several of the newly included studies containing PM<sub>2.5</sub> were from cities in China where much higher PM<sub>2.5</sub> levels (e.g. 38–71 µg/m<sup>3</sup>) were reported [36, 39]. This is in sharp contrast to earlier studies that were conducted in cities with much lower pollution levels (e.g., 4–14 µg/m<sup>3</sup>).

This phenomena of decreasing effect size with increasing PM<sub>2.5</sub> concentrations has been previously documented [40], which indicates a non-linear association between concentration and response. Nonetheless, our findings are supported by existing literature on the impact of ambient air pollution on stunting defined as HAZ. A recent study found that prenatal exposure to the 1997 Indonesian forest fires is associated with a 0.41 in HAZ (or 3.4 cm) at age 17, which implies a loss of 4% of average monthly wages for approximately 1 million Indonesian workers born during this period [41]. Another study reported that in Bangladesh, where stunting prevalence is as high as 36%, children with a high quartile of PM<sub>2.5</sub> exposure (52–73 µg/m<sup>3</sup>) had 1.13 times the risk of stunting (HAZ < - 2) than that of children in the lowest quartile of exposure [23].

For household air pollution, we identified five epidemiologic studies for moderate and severe stunting defined by HAZ, including three studies published after a previous meta-analysis [14]. Bruce et al. [14] reported a pooled OR of 1.27 (95% CI: 1.12–1.43) for moderate and severe stunting associated with household air pollution from cooking with solid fuels. Similar to the pooled estimates for ambient air pollution, our pooled effect estimates for household air pollution from cooking with solid fuels are smaller, but nonetheless in the same direction of association. The volume of evidence from both ambient and household particulate exposure suggests a high level of confidence regarding causality between ambient particulate pollution and prenatal determinants of stunting.

There is a strong biological basis for the relationship between air pollution exposure and low birthweight. Kannan et al. [42] reviewed the evidence from existing literature and determined there are potentially five distinct mechanisms at work: oxidative stress, inflammation, coagulation, endothelial function and hemodynamic responses. While precise biological mechanisms connecting air pollution with impaired fetal growth are unknown, it is commonly hypothesized that transplacental and postnatal exposure to particulate matter may result in oxidative stress leading to DNA damage. Induced acute placental and pulmonary inflammation, increased possibility for coagulation, and triggered endothelial dysfunction are also hypothesized biological mechanisms.

Our meta-analysis had several limitations. First, we observed a moderate to high degree of heterogeneity across gestational exposure periods and exposure metrics. Such heterogeneity may be explained by differences in study design methods and exposure assessment, covariate adjustment, study population and/or PM chemical composition that varies by study location. Further studies are needed to explore the independent and joint effects of early life exposures to air pollution and nutrition, and the effect of PM constituents on stunting-related risks. Second, we did not evaluate studies with other exposure periods (e.g., months) due to scarcity of relevant studies. Hence our observed effects on stunting-related risks based on the entire pregnancy period and specific trimester periods may not infer biological significance as for timing over gestation. Moreover, while majority of the included studies evaluated stunting-related outcomes as categorical measures (e.g., HAZ < - 2 SD), it is important to note that growth faltering is a gradient, and children above the conventional cut-off points for SGA/IUGR/HAZ may still experience suboptimal linear growth, especially in low-resource settings [7, 12], and thus the actual impact of air pollution on stunting or growth failure may be underestimated. Last but not least, we did not assess the quality of each included study.

These limitations are balanced by the substantial strengths of our study. While much of the material in this review has been published previously, additional value derives from updating existing reviews (seven versus 26 for ambient PM pollution in the current review, three versus nine for household air pollution) using comparable methods, including effects from both the continuous and categorical measures of PM<sub>2.5</sub> and PM<sub>10</sub> exposures. Prior to this review, an effort to join all available childhood stunting-related outcomes, as well as both the ambient particulate pollution exposure and household air pollution from solid fuel, had not been attempted. Our pooled estimates were robust in sensitivity analyses, as demonstrated by using stricter definitions of stunting, or removing one study from the main analysis. There was also no significant publication bias according to Begg's and Egger's tests.

## Conclusions

Based on a meta-analysis of 31 eligible studies on the association of air pollution and stunting-related outcomes, we found new evidence of increased risk of prenatal determinants of stunting associated with ambient PM<sub>2.5</sub> exposure during pregnancy, especially the first trimester, as well as suggestive evidence of elevated stunting risk with postnatal exposure to household air pollution. Eligible studies reflect a much greater range of exposures than those examined in the previous systematic reviews, and also include studies conducted in countries where both adverse pregnancy outcomes and stunting are major public health challenges. Findings suggest the importance of promoting clean air as part of an integrated approach to preventing stunting. Given the critical importance of prenatal determinants of stunting, emerging evidence provides an additional public health imperative to improve air quality. For example, in India, a country with one of the highest stunting prevalence (38%) among children under 5 and the highest SGA prevalence (37%) among live births [43, 44], reducing the annual mean PM<sub>2.5</sub> concentration from 91 µg/m<sup>3</sup> in 2017 to WHO air quality guideline levels (10 µg/m<sup>3</sup>) would result in more than 1.8 million or 20% fewer children born SGA in India.

## Abbreviations

CI: Confidence interval; HAZ: Height-for-age z score; IUGR: Intrauterine growth retardation; OR: Odds ratio; PM: Particulate matter; PM<sub>10</sub>: particulate matter with aerodynamic diameter less than 10 µm; PM<sub>2.5</sub>: Particulate matter less than 2.5 µm in diameter; SD: Standard deviations; SGA: Small for gestational age; WHO: World Health Organization

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable

### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Competing interests

The authors declare that they have no competing interests.

### Funding

No funding was received.

### Authors' contributions

VP conducted literature review, prepared the datasets, interpreted the results and drafted and finalized the manuscript; RD contributed to literature review, dataset preparation, and results interpretation; SM contributed to the conception of the meta-analysis, interpreted the findings and assisted in drafting the manuscript. All authors have read and approved the manuscript.

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## Figures

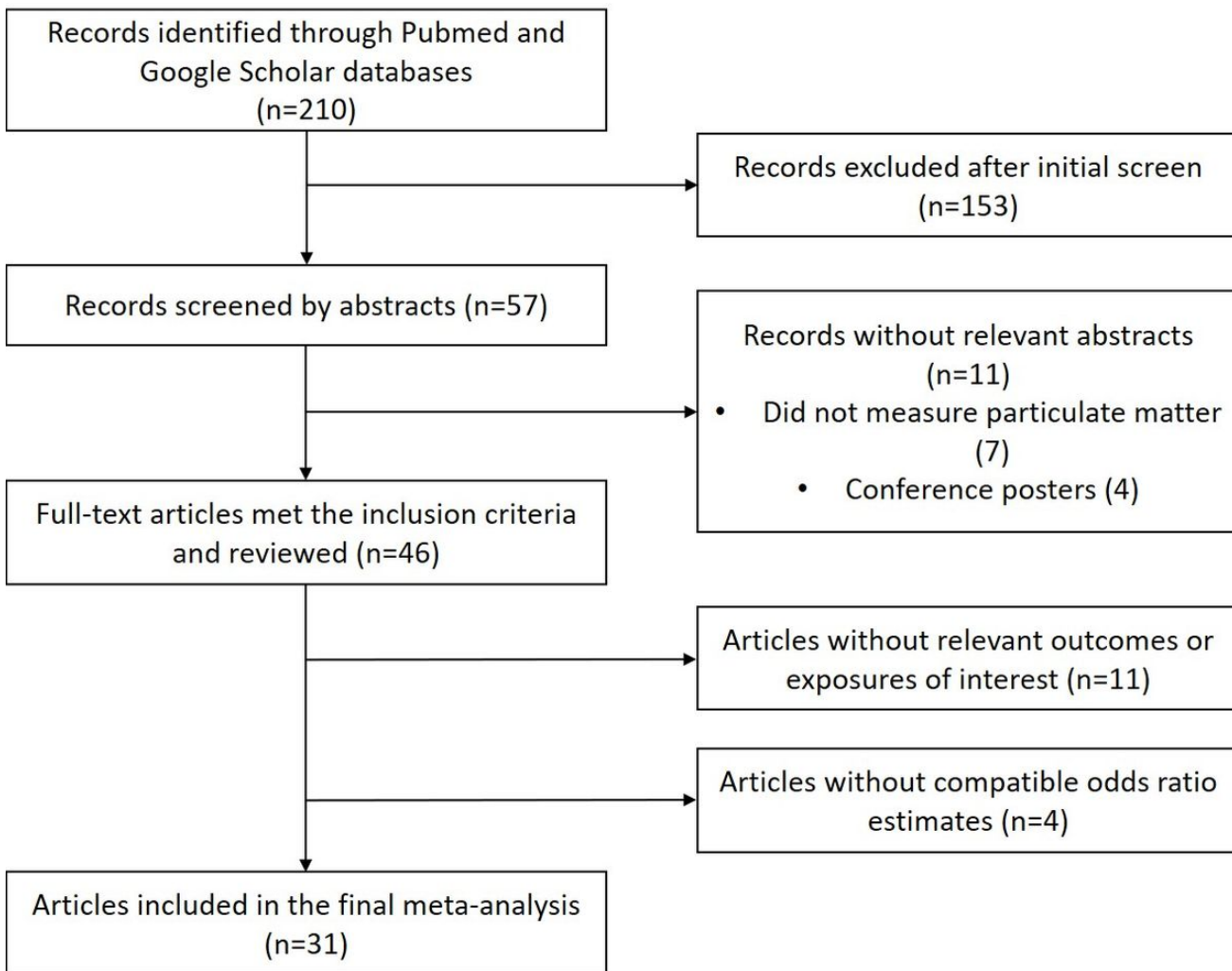


Figure 1

Flow diagram of included/excluded studies

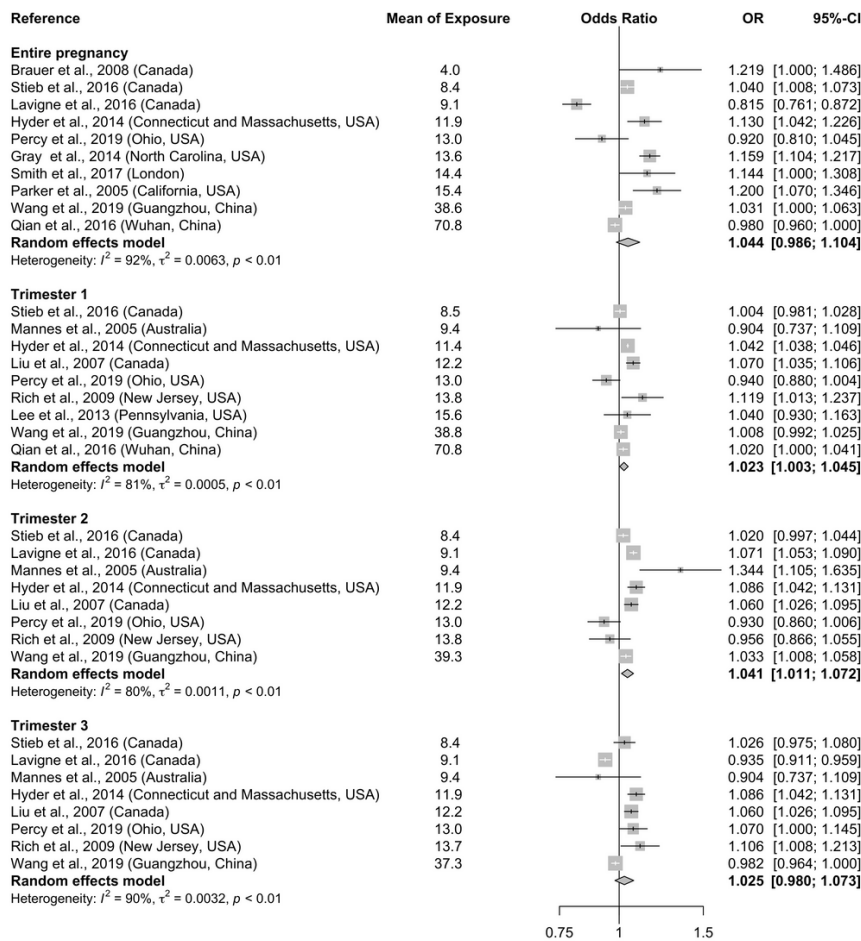


Figure 2

Odds ratios and 95% confidence intervals (CI) for stunting per 10  $\mu\text{g}/\text{m}^3$  increase in ambient  $\text{PM}_{2.5}$  concentration, by exposure period; pooled estimates of odds ratios are indicated by vertical points of diamonds and 95% CI are represented by horizontal points; size of shaded area around point estimate is proportional to weight in calculating pooled estimate.

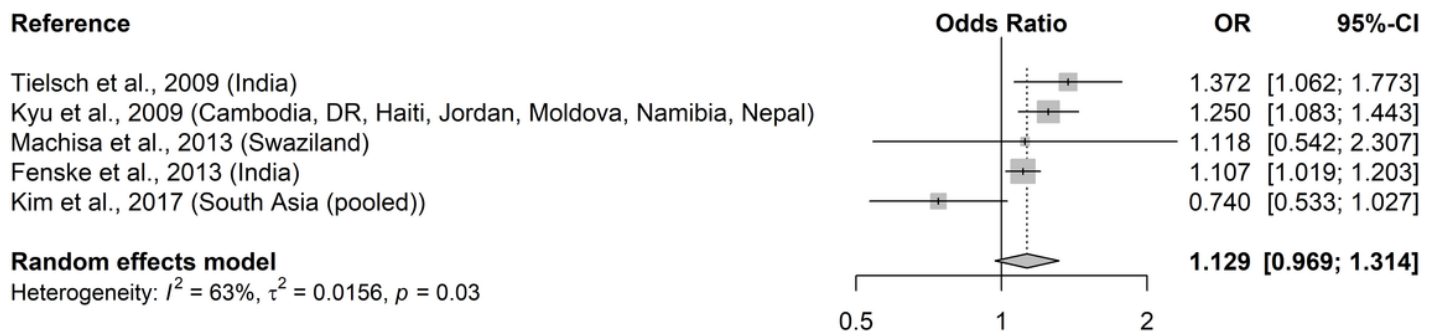


Figure 3

Odds ratios and 95% confidence intervals (CI) for stunting associated with exposure to household air pollution from solid fuel use compared with cleaner fuels during entire pregnancy; pooled estimates of odds ratios are indicated by vertical points of diamonds and 95% CI are represented by horizontal points; size of shaded area around point estimate is proportional to weight in calculating pooled estimate.

## Supplementary Files

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