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Review article

An exposure-response meta-analysis of ambient $PM_{2.5}$ during pregnancy and preeclampsia

Priyanka Gogna [a,*], Paul J. Villeneuve [b], Michael M. Borghese [a,c], Will D. King [a]

[a] Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada
[b] School of Mathematics and Statistics, Carleton University, Ottawa, Ontario, Canada
[c] Environmental Health Science and Research Bureau, Health Canada, Ottawa, Ontario, Canada

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ABSTRACT

Relationships between $PM_{2.5}$ exposure and preeclampsia have been the focus of four recent systematic reviews and meta-analyses. We expand on knowledge gaps in these reviews by characterizing the shape of the exposure-outcome relationship, and by assessing the heterogeneity in these associations by study characteristics. Studies of $PM_{2.5}$ and preeclampsia were identified from reviews, and confounder-adjusted estimates were extracted. Estimates were derived using a random-effects model. Potential non-linearity was evaluated using a one-stage dose-response meta-analysis. Contrary to previous meta-analyses reporting stronger relationships, the overall adjusted relative risk (RR) for a 10 $\mu g/m^3$ average increase in $PM_{2.5}$ during pregnancy and preeclampsia was modest and not statistically significant (RR: 1.07, 95% CI: 0.99–1.15). This was mainly attributable to inclusion/exclusion decisions for studies made during this review. In addition, there was no evidence of non-linearity, and no important sub-group differences by characteristics such as region, exposure assessment, participant exclusions, and early versus late-onset preeclampsia. Overall, our analysis suggests a modest relationship between ambient $PM_{2.5}$ and preeclampsia. We provide details on inclusion and exclusion decisions that were lacking in previous studies, and report novel investigations of non-linearity and heterogeneity.

1. Introduction

Preeclampsia is defined by the presence of hypertension and target organ involvement at minimum 20 weeks into pregnancy (Butalia et al., 2018). Damaged blood vessels lead to effects such as increased vascular permeability, which causes a cascade of other effects and complications such as endothelial leakage, renal lesions, and edema, damaging organs such as the kidneys, liver, lungs, and brain (Hladunewich et al., 2007; Stillman and Karumanchi, 2007). Preeclampsia impacts an estimated 2–8% of pregnancies worldwide, and is responsible for 10–15% of maternal deaths (Duley, 2009). Although preeclampsia typically resolves at, or shortly after delivery, complications arising from preeclampsia can have long-term impacts on the health of the mother and child. These impacts include increased risks of cardiovascular disease and diabetes in the mother, as well as preterm birth and reduced infant growth (Butalia et al., 2018; Davies et al., 2016; Kokubo and Matsumoto, 2017; Sibai, 2005). Risk factors for preeclampsia have been extensively studied, and include nulliparity (Steegers et al., 2010), older age (Steegers et al., 2010), higher body mass index (Steegers et al., 2010), family history of preeclampsia (Steegers et al., 2010), multiple pregnancy (Steegers et al., 2010), underlying medical conditions (Steegers et al., 2010), smoking (Shamsi et al., 2013), and nutrition (Dasinger et al., 2020), as well as environmental risk factors such as lead exposure (Poropat et al., 2018), and other contaminants (Dasinger et al., 2020).

Ambient air pollution has been associated with pregnancy complications, including preeclampsia. $PM_{2.5}$ (particulate matter with diameter <2.5 μm) is a commonly measured outdoor air pollutant, and is an established risk factor for several health outcomes. It represents a complex mixture containing a number of harmful solid and liquid airborne particles resulting from chemical reactions in the atmosphere, and through fuel combustion. The composition of $PM_{2.5}$ can differ based on region, and has been shown to have differing impacts on health outcomes based on composition (Dadvand et al., 2013b; National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020). Some studies of $PM_{2.5}$ have also considered various measures of exposure, including separating out the components of $PM_{2.5}$ or modelling traffic sources of $PM_{2.5}$, however this work has been limited, and with

* Corresponding author. 62 Fifth Field Company Lane, Department of Public Health Sciences, 2nd Floor, K7L 3L3, Kingston, ON, Canada.
E-mail address: gogna.p@queensu.ca (P. Gogna).

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heterogenous measures of $PM_{2.5}$ source used (Dadvand et al., 2014; Ibrahimou et al., 2014; Mandakh et al., 2020; Mendola et al., 2016; Michikawa et al., 2021; Wu et al., 2009). Preeclampsia is characterized by an exaggerated pro-inflammatory response. Higher exposure to $PM_{2.5}$ is also associated with higher levels of circulating pro-inflammatory and oxidative stress markers and endothelins, and therefore may exacerbate the maternal endothelial response in the progression of preeclampsia (Agrawal et al., 2018; Lee et al., 2011; Mostafavi et al., 2015; Suhaimi and Jalaludin, 2015; Tang et al., 2020; van den Hooven et al., 2012; et al., 2021).

Previous studies on the relationship between $PM_{2.5}$ exposure and preeclampsia have been summarized in three recent systematic reviews and meta-analyses, along with a monograph published by the National Toxicology Program (NTP) (Bai et al., 2020; National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020). These studies reported the following estimates of effect for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure and risk of developing preeclampsia: Bai et al. 1.08 (95% CI: 0.97–1.18), Sun et al., 1.31 (95% CI: 1.07–1.61), NTP Monograph: 1.51 (95% CI: 1.04–2.20), and Yu et al., 1.32 (1.10–1.58). However, these reviews used slightly different inclusion criteria, such as for estimates of traffic-specific versus ambient $PM_{2.5}$, and for estimates reported in different published papers of the same study populations. These decisions may have impacted effect estimates, however, the reviews did not consistently provide their rationale for inclusion decisions. In addition, knowledge gaps remain for the relationship of interest, including the shape of the exposure-response relationship and an evaluation of the high degree of heterogeneity observed in averaged estimates. Previous studies of the effects of air pollution on health outcomes have shown that relationships between $PM_{2.5}$ exposure and health outcomes may be non-linear (Brauer et al., 2019; Christidis et al., 2019; Crouse et al., 2019; Filippini et al., 2015; Pappin et al., 2019; Pope et al., 2011). Understanding non-linearity in these relationships is important for implementation of policy decisions to reduce population-level exposures. To our knowledge, no studies have assessed the relationship between $PM_{2.5}$ and preeclampsia using formal techniques to evaluate non-linearity, despite methods available to investigate non-linearity across studies using single linear estimates from individual studies (Crippa et al., 2019). Furthermore, individual studies conducted over one geographic region tend to be limited in their ability to evaluate dose-response relationships as their population exposure distribution may not cover a sufficient portion of the exposure-response curve. In the past decade, exposure-response meta-analysis techniques have been developed to assess non-linearity, where information on the population exposure, and exposure-disease relationships can be combined across studies, even in the absence of categorized exposure estimates within studies (Crippa and Orsini, 2016). However, meta-analyses assessing the relationship between $PM_{2.5}$ and preeclampsia have not used these modern methods to evaluate non-linearity (Bai et al., 2020; National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020).

The current study aims to expand on recently published systematic reviews and meta-analyses of the relationships between $PM_{2.5}$ and preeclampsia with an investigation of non-linear exposure-response, heterogeneity of effects by geographic region, exposure assessment method, exclusion of participants with pre-existing hypertension, and early versus late onset preeclampsia. Our research question formulated as a PECO statement (Morgan et al., 2018) is as follows: Is higher ambient $PM_{2.5}$ exposure (**E**xposure and **C**omparator) in pregnant women (**P**opulation) associated with the risk of developing preeclampsia (**O**utcomes), and is there non-linearity or heterogeneity of effects by study and population characteristics in this relationship? We followed all applicable PRISMA Guidelines for Systematic Reviews and Meta-Analyses for this review (Moher et al., 2009). As we primarily relied on data presented in recently published systematic reviews, a review protocol was not registered.

2. Methods

2.1. Study collection strategy

Four recently published systematic reviews and meta-analyses were reviewed, and their inclusion and exclusion criteria were deemed sufficiently overlapping with our research question to justify use of these studies for identifying relevant papers for the relationship between $PM_{2.5}$ and preeclampsia (Bai et al., 2020; National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020). Each review selected a different number of eligible studies, and all original studies of $PM_{2.5}$ and preeclampsia from each review were identified. In addition, we used the following search criteria to update the search using Ovid Medline and PubMed databases (June 14th, 2021): "((pm OR particulate matter) AND (preeclampsia OR hypertension OR gestational hypertension))". We used a filter for English language studies conducted since 2019 to capture any articles published after the search dates provided in the recent reviews (earliest search date: January 28th, 2019 by NTP Monograph). The titles of 244 articles were screened in Ovid Medline, and 537 articles in Pubmed.

2.2. Selection criteria

Inclusion criteria for papers of interest to this review were as follows: 1.) Peer reviewed, original research articles (no conference abstracts), 2.) Studies conducted in human female populations during pregnancy, 3.) Prospective or retrospective cohort studies, or case-control studies, 4.) Studies assessing total ambient (outdoor) $PM_{2.5}$ as the exposure and preeclampsia as the outcome of interest.

The following exclusion criteria were applied: 1.) Non-English language studies, 2.) Studies not reporting a measure of effect, or a measure with no 95% confidence interval (CI), variance, or standard error.

2.3. Screening and data extraction

Relevant study characteristics along with measures of effect and 95% CIs were extracted from each primary study. Where there was ambiguity, estimates were extracted in duplicate by a second author (WDK), and consensus was reached regarding inclusion of a summary estimate.

Measures of effect controlling for the largest set of potential confounders were extracted where multiple estimates were presented. Where studies reported estimates that were limited to specific time-windows and not the pregnancy average, the available estimate was still extracted and assumed to represent pregnancy-average exposure. This was done in order to maximize the number of studies that could be included, and was in line with methods used in three of the previous reviews (National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020). Where multiple exposure windows were reported with no pregnancy-average estimates, effects and 95% CIs were averaged to create an overall estimate that could be used to represent the effect of pregnancy-average $PM_{2.5}$ exposure. Extracted estimates were transformed to represent the linear increase in risk per 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure.

2.4. Meta-analyses

Measures of effect and 95% CIs from included studies were initially combined using a random-effects model, using only estimates based on the assumption of a log-linear relationship between $PM_{2.5}$ and preeclampsia from each study.

Deviation from a summary linear exposure-response relationship across all studies between $PM_{2.5}$ and preeclampsia was investigated with a one-stage dose-response meta-analysis approach (Crippa et al., 2019), using restricted cubic splines (RCS) with knots placed at 2 $\mu g/m^3$, 10 $\mu g/m^3$, and 22 $\mu g/m^3$ along the exposure distribution (corresponding approximately to the 10th, 50th, and 90th percentiles of the exposure

distribution). This method is a recently developed extension of the traditional two-stage dose-response meta-analysis. Briefly, two different approaches have been commonly used to study a summary estimate of log-linear trend in meta-analysis (Crippa et al., 2019; Greenland and Longnecker, 1992). A two-stage approach first estimates study-specific trends, and then combines these using a meta-analysis (Greenland and Longnecker, 1992). In contrast, a one-stage approach extracts category specific effects and category midpoints where available, and an effect estimate and mean exposure for a continuous metric where that is the only effect available, and combines these effects in a meta-analysis (Crippa et al., 2019). The main advantage of the latter is in evaluating and estimating non-linear trends where there is a mix of continuous and categorical exposure estimates in the literature of interest.

The method fits a mixed effects RCS model taking into account the correlation within sets of published estimates for each study where multiple estimates are available (Crippa et al., 2019). For this analysis, categorized exposure estimates were extracted from studies where available, and combined with estimates per unit increase in $PM_{2.5}$ from remaining studies. Finally, to aid in the interpretation of the dose-response meta-analysis, studies were categorized into "low" ($\leq$10 $\mu g/m^3$) and "high" (>10 $\mu g/m^3$) exposure groups and combined measures of effect were estimated in a sub-group analysis. This cut-off corresponded with previous WHO guidelines which had been in effect from 2006 to 2021 (World Health Organization, 2006). In 2021, guidelines were changed to recommend that annual $PM_{2.5}$ levels not exceed an annual mean of 5 $\mu g/m^3$, however this would not have left enough data points in our analysis to study differences in effect (World Health Organization, 2021). All analyses were conducted in R version 3.6.3, using the R packages metafor (Viechtbauer, 2010), dmetar (Harrer et al., 2019), and dosresmeta (Crippa and Orsini, 2016).

Where some exposure distribution information was missing for studies (IQR, 1st and 3rd quartiles, or median), a normal distribution of $PM_{2.5}$ was assumed to help categorize whether the study population belonged to a high or low exposure group and to identify quartile cut-points for the dose-response meta-analysis. In addition, if studies did not report the number of cases per quartile categorization in non-linearity assessments, case numbers were estimated based on the measures of effect reported for each category.

In heterogeneity analyses, differing measures of effect by exposure-related variables, including geographic region and exposure assessment, and outcome-related variables, including exclusion of participants with pre-existing hypertension and early versus late onset preeclampsia were estimated. Some studies in this literature have excluded participants with pre-existing hypertension. This may be inappropriate because both chronic and gestational hypertension are risk factors for the development of preeclampsia (Steegers et al., 2010), and because air pollution is positively associated with a higher risk of developing hypertension (Qin et al., 2021). We felt it was important to investigate the impact that these exclusion decisions would have on effect estimates in a sensitivity analysis.

Heterogeneity by time-window was also investigated among studies reporting trimester-specific results. Effect estimates presented as a continuous increase in $PM_{2.5}$ and preeclampsia reported in each study were used for sub-group analyses. Heterogeneity was quantified using the I^2 statistic (Higgins and Thompson, 2002) in addition to a formal χ^2 test.

Publication bias was assessed using Egger's weighted linear regression test (Egger et al., 1997). Leave-one-out analyses were also conducted to assess the impact of individual studies on the combined estimates for the overall relationship (Patsopoulos et al., 2008).

3. Results

3.1. Studies description and extraction

Twelve unique studies were identified across all reviews (Tables A1). In Tables A2 and A3 we contrast studies included in this review with those in other meta-analyses. Of the studies included in our review, two pairs of analyses were conducted on the same populations (Dadvand et al., 2013a, 2014; Wu et al., 2009, 2011). However, in each pair, one study focused on total ambient $PM_{2.5}$ while the second focused on local, traffic-generated exposures. Therefore, following the exclusion criteria defined above, we excluded studies that focused on traffic-related $PM_{2.5}$ levels (Dadvand et al., 2014; Wu et al., 2009). Mandakh et al. (2020) provided estimates based on local and total $PM_{2.5}$ levels. For this analysis, the estimate based on total $PM_{2.5}$ levels was used.

Three additional studies were identified via title and abstract screening of recent studies in Pubmed and Ovid Medline (Daniel et al., 2021; Jia et al., 2020; Weber et al., 2021). Two of these studies were included (Daniel et al., 2021; Weber et al., 2021), and one study was excluded (Jia et al., 2020) as the population exposure estimate represented an extreme outlier in the range of doses present among remaining studies (maximum dose including Jia et al.: 111.67 $\mu g/m^3$, without Jia et al.: 20.37 $\mu g/m^3$).

A final set of twelve studies were therefore eligible for inclusion (Table 1). Studies tended to control for a comprehensive set of potential confounders, with a focus on established risk factors for preeclampsia, including maternal age, BMI, alcohol consumption, smoking, race/ethnicity, season, neighbourhood deprivation index, education, and income. Some studies controlled for pre-existing conditions such as diabetes or hypertension. Detailed information on confounders controlled for in each study are provided in Table A4. The definition of the outcome was relatively consistent, and the majority of studies defined preeclampsia based on the International Classification of Disease (World Health Organization, 2009) codes for mild and severe preeclampsia, as well as eclampsia (Assibey-Mensah et al., 2020; Choe et al., 2018; Dadvand et al., 2013a; Daniel et al., 2021; Mandakh et al., 2020; Mendola et al., 2016; Nobles et al., 2019; Savitz et al., 2015; Weber et al., 2021). One study included HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count) in their definition (Wu et al., 2009), one study used the American College of Obstetricians and Gynecologists definition (Rudra et al., 2011), and one study defined preeclampsia as gestational hypertension accompanied by proteinuria after 20 weeks of gestation (Lee et al., 2013).

As the outcome of interest was rare across studies, final averaged effect estimates were interpreted as relative risks (RR) in this investigation. When measures of effect were reported by groupings representing unique sets of individuals (early versus late preeclampsia, estimates from distinct populations being presented in the same paper, other interaction analyses), separate estimates were extracted from studies and included in analyses, as done in two of the previous reviews (Bai et al., 2020; National Toxicology Program (NTP), 2019). For example, two papers reported separate estimates for distinct populations within the same study (Daniel et al., 2021; Wu et al., 2009). These were considered separate estimates in analyses (Wu et al., 2011: a = Los Angeles, b = Orange County, Daniel et al., 2021: a = Jewish women, b = Bedouin women). One study reported measures of effect by asthma status only (Mendola et al., 2016), and therefore two measures of effect were extracted from this study and included in the meta-analysis (Mendola et al., 2016: a = no asthma, b = asthma).

One study reported estimates for the first and second trimesters only and mild versus severe preeclampsia only (Savitz et al., 2015). For this study, measures of effect were averaged across reported trimesters for both mild and severe (Savitz et al., 2015: a = mild, b = severe) preeclampsia groups, and both measures of effect were included in the main analyses. One study reported estimates for mild and severe preeclampsia separately with no overall estimate, and therefore these estimates were included separately in the analysis (Weber et al., 2021: a = mild, b = severe) Although two distinct estimates each were extracted from Savitz et al. and Weber et al., where reference groups were the same within studies, the estimates represented distinct cases and instances where the precision of estimates was primarily driven by cases due to a low disease

Table 1
Study characteristics of included studies for the relationship between $PM_{2.5}$ and preeclampsia.

First Author & Year	Study design	Location	Year(s) of data collection	Outcome Assessment Method	Exposure assessment method	Cases/ Cohort Size	Consideration of non-linear relationships?	Consideration of early versus late preeclampsia status?	Exclusion of women with chronic hypertension/ superimposed preeclampsia/ eclampsia?
Wu et al. (2011)	Cohort	California, USA	1997–2006	Medical records	Ground monitor	2442/ 81,186	No	No	No
Rudra et al. (2011)	Cohort	Washington State, USA	1996–2006	Clinical data	Modelling approach	117/ 3509	Yes	No	No
Lee et al. (2013)	Cohort	Pennsylvania, USA	1997–2002	Medical records	Ground monitor	699/ 34,705	No	No	Yes
Dadvand et al., 2013a	Cohort	Barcelona, Spain	2000–2005	Medical Records	Modelling approach	103/ 8398	No	Yes	No
Savitz et al. (2015)	Cohort	New York, USA	2008–2010	Medical records	Modelling approach	11,166/ 268,601	Yes	Yes	Yes
Mendola et al. (2016)	Cohort	USA	2002–2008	Medical records	Modelling approach	10,528/ 210,508	No	Yes[a]	Yes
Choe et al. (2018)	Cohort	Rhode Island, USA	2002–2012	Medical records and birth certificate	Modelling approach	2221/ 61,640	No	No	No
Nobles et al. (2019)	Cohort	Utah and Idaho, USA	2002–2010	Medical records	Modelling approach	1712/ 49,607	No	No	Yes
Mandakh et al. (2020)	Cohort	Southern Sweden	2000–2009	Medical records	Modelling approach	1034/ 35,570	Yes	Yes	No
Assibey Mensah et al. (2020)	Cohort	New York, USA	2009–2013	Medical records	Ground monitor	732/ 16,116	No	Yes	Yes
Daniel et al. (2021)	Cohort	Israel	2004–2016	Medical records	Modelling approach	2.202/ 133,197	No	Yes[a]	No
Weber et al. (2021)	Case-control	California, USA	2000–2006	Medical records	Ground monitor	2026/ 75,124	No	Yes	Yes

Where there were differences, numbers were based on pregnancies, not women.
[a] Authors assessed early versus late onset preeclampsia, but quantitative results not reported.

prevalence (Savitz et al., 2015; Weber et al., 2021).

For evaluation of time windows of exposure, different exposure windows evaluated in each study were averaged to represent pregnancy-average exposures. One study reported a final month of pregnancy estimate rather than a third trimester estimate. This result was used as the third trimester estimate for analyses (Wu et al., 2011). Two studies reported effect estimates during early pregnancy only (Lee et al., 2013; Rudra et al., 2011). These measures of effect were used to represent the pregnancy-average relationship for these studies, under the assumption that the relationship between $PM_{2.5}$ and preeclampsia is the same throughout pregnancy. One study reported estimates only by weeks of gestation, and these weekly estimates were averaged to compute an overall estimate, and first and second trimester estimates (Daniel et al., 2021). Three studies provided estimates for multiple exposure windows during pregnancy without a pregnancy-average exposure window, and therefore estimates were averaged across exposure windows within each study to represent a pregnancy-average exposure (Assibey-Mensah et al., 2020; Choe et al., 2018; Rudra et al., 2011).

Two studies (Savitz et al., 2015; Weber et al., 2021) reported estimates based on mild versus severe preeclampsia. As mild and severe preeclampsia typically corresponds with the timing of preeclampsia diagnosis during the pregnancy, estimates from this study for mild and severe were used as proxies for late and early onset preeclampsia, respectively, in the sub-group analysis (Savitz et al., 2015; Weber et al., 2021).

3.2. Overall and dose-response meta analyses

The overall combined RR for a 10 $\mu g/m^3$ increase in pregnancy-average $PM_{2.5}$ exposure and preeclampsia risk was 1.07 (95% CI: 0.99–1.15), estimated using a random effects model. There was heterogeneity across studies ($I^2 = 0.70$, p-value<0.01) (Fig. 1).

A one-stage dose-response meta-analysis was conducted to evaluate potential non-linearity in the relationship between $PM_{2.5}$ and preeclampsia. Four studies reported categorized estimates to include in analyses (Mandakh et al., 2020; Rudra et al., 2011; Savitz et al., 2015; Weber et al., 2021), and continuous estimates, along with population median/mean $PM_{2.5}$ values were extracted from remaining studies for analysis.

Knots were placed at 2 $\mu g/m^3$, 10 $\mu g/m^3$, and 22 $\mu g/m^3$ along the exposure distribution. This categorization approximately corresponded with the 10th, 50th, and 90th percentiles typically used in RCS analyses, and was consistent with planned sub-group analysis at a cut-off of 10 $\mu g/m^3$. The RCS analysis did not suggest non-linearity in the exposure-outcome relationship (Fig. 2). The RCS model had poorer model fit compared to the model assuming a log-linear relationship (AIC: −0.43 versus −7.99).

As direct interpretation of beta-estimates from RCS analyses is difficult, we chose to further explore non-linearity based on categorization of studies into low and high exposure groups, based on previous WHO guidelines (10 $\mu g/m^3$). Thirteen measures of effect from eight studies were categorized into the high exposure group (mean/median $PM_{2.5}$ levels >10 $\mu g/m^3$), and the remaining four studies were categorized into the low exposure group (≤10 $\mu g/m^3$). The averaged effect estimate from both exposure groups were similar (≤10 $\mu g/m^3$ RR: 1.03, >10 $\mu g/m^3$ RR = 1.07). The heterogeneity p-value for this analysis was not statistically significant (p-value: 0.68) (Fig. 2).

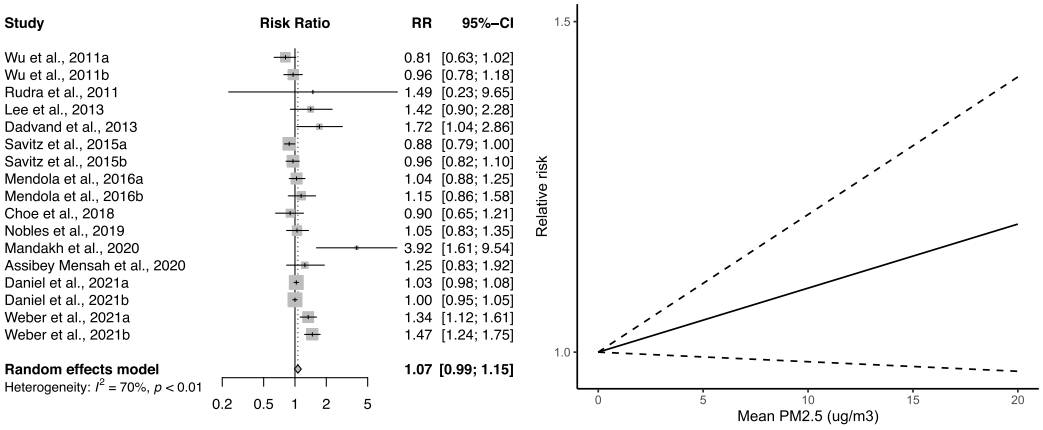

Fig. 1. Forrest plot of studies for the relationship between $PM_{2.5}$ and preeclampsia presented on the left (per 10 μg/m^3 increase). Squares represent relative weights of each study. Meta-regression plot assuming a linear relationship between $PM_{2.5}$ and preeclampsia risk is presented on the right.

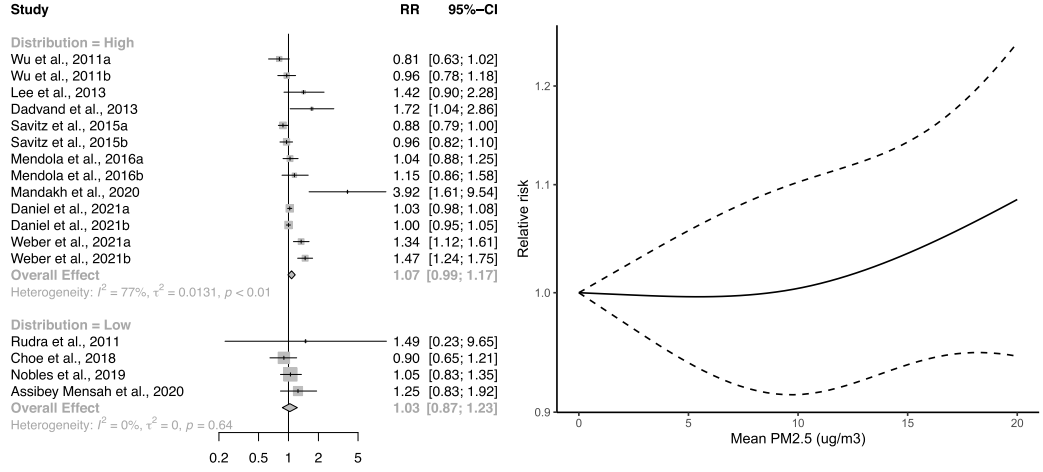

Fig. 2. Sub-group analyses of studies for the relationship between $PM_{2.5}$ and preeclampsia ("high exposure" defined as greater than 10 μg/m^3) presented on the left (per 10 μg/m^3 increase, random effects model) (test for subgroup differences p-value = 0.68). Squares represent relative weights of each study. One-stage dose-response meta-analysis of relationship between $PM_{2.5}$ and preeclampsia (knots at 2 μg/m^3 percentile, 10 μg/m^3, and 22 μg/m^3 of the distribution) presented on the right. The one-stage dose-response meta-analysis was based on extraction of estimates for categorization of $PM_{2.5}$ exposure where available.

3.3. Sub-group analyses

Sub-group analyses are presented in Figs. 3 and 4. Sub-group analyses for differences in effect by study region, exposure assessment, exclusion of participants with pre-existing hypertensive disorders, and early vs. late onset preeclampsia were not appreciably different, and did not indicate differences by subgroups (Figs. 3 and 4).

We also conducted sub-group analyses by trimester of exposure. Effect estimates were homogeneous, with overlapping confidence intervals (Trimester 1: 1.01 [95% CI: 0.95–1.07], Trimester 2: 1.00 [0.95–1.04], Trimester 3: 1.13 [95% CI: 0.97–1.32]) (Fig. 5).

Overall, there was substantial heterogeneity in summary measures in the main analysis, which remained unresolved within subgroups evaluated.

3.4. Publication bias and sensitivity analyses

Egger's weighted linear regression test was non-significant, concluding lack of evidence for publication bias (p = 0.12). Results for leave-one-out analyses are presented in Figure A1, and did not suggest that any single analysis had undue influence on the analysis results.

4. Discussion

In this review, we sought to expand on systematic reviews and meta-analyses of $PM_{2.5}$ and preeclampsia by assessing non-linearity in the exposure-response relationship, and the heterogeneity of effects by study characteristics. Overall, a RR of 1.07 (95% CI: 0.99–1.15) for the effect between a 10 μg/m^3 increase in $PM_{2.5}$ exposure and risk of preeclampsia was estimated, suggesting a modest association between ambient $PM_{2.5}$ and preeclampsia. In addition, we did not find evidence of non-linearity in this relationship in the dose-response meta-analysis, and there was substantial heterogeneity of effects across studies for the relationship of interest.

We did not find differences in the effect estimates when assessing different exposure windows. As there is limited evidence for differences in effect by exposure window during pregnancy, we assessed pregnancy average exposures in the main analysis to maximize study power. Where different exposure windows were assessed in studies, there was heterogeneity in exposure windows used (Daniel et al., 2021; Lee et al., 2013; Rudra et al., 2011; Wu et al., 2011), and formal statistical analyses of differences was limited due to the same pregnancy cohorts being used to assess these differences.

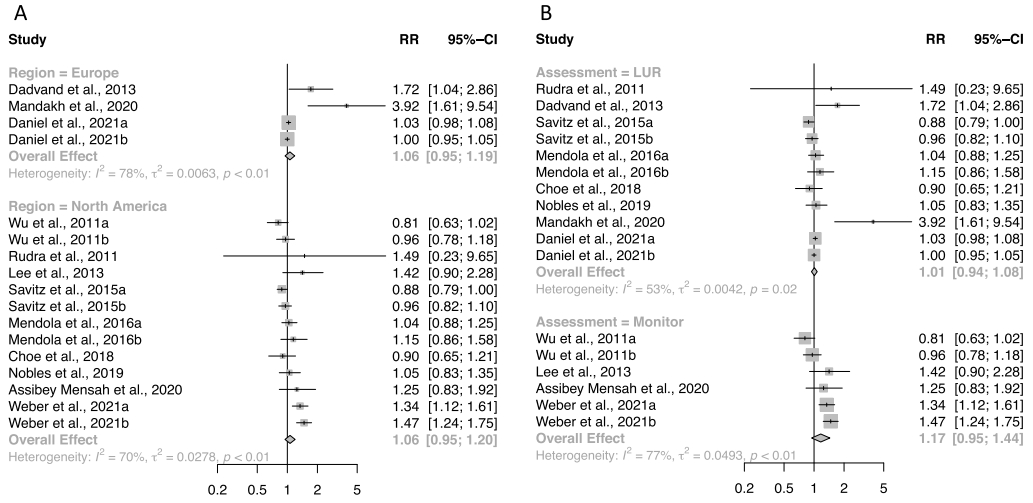

Fig. 3. Subgroup analyses by exposure characteristics for relationships between $PM_{2.5}$ and preeclampsia. A: By study region (test for subgroup differences p-value = 0.96), B: By assessment type (test for subgroup differences p-value = 0.19). Squares represent relative weights of each study.

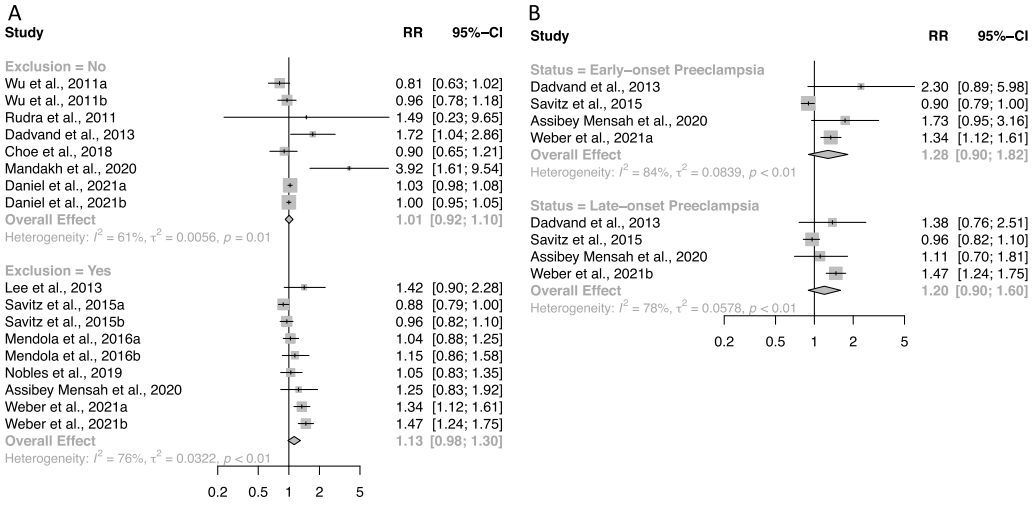

Fig. 4. Subgroup analyses by outcome characteristics for relationships between $PM_{2.5}$ and preeclampsia. A: By exclusion of participants with pre-existing hypertensive disorders (test for subgroup differences p-value = 0.18), B: By early versus late-onset preeclampsia status for relationship between $PM_{2.5}$ and preeclampsia (test for subgroup differences p-value = 0.77). Squares represent relative weights of each study.

We noted that some studies suggest a relationship between more specific traffic-based $PM_{2.5}$ and traffic-related components of $PM_{2.5}$. These studies are described in Table A5, with details on exposure assessment for each study. An American study published an analysis of traffic-based $PM_{2.5}$ exposures based on modelling and reported a RR of 1.11 (95% CI: 1.06–1.15) per IQR increase (Wu et al., 2009), and a similar study assessing local $PM_{2.5}$ exposure in Sweden found an RR of 2.74 (95% CI: 1.68–4.47) per IQR increase (Mandakh et al., 2020). However, a similar source-based analysis conducted in Spain for traffic-related $PM_{2.5}$ exposure and preeclampsia did not find a strong or statistically significant relationship (RR: 1.03, 95% CI: 0.64–1.64) (Dadvand et al., 2014).

Three previous studies (Ibrahimou et al., 2014; Mendola et al., 2016; Michikawa et al., 2021) found stronger effects when assessing carbon as a chemical constituent of $PM_{2.5}$ and preeclampsia risk (Supplementary Table A5, effect estimates between 1.01 and 1.15). Qualitatively, these results appear to be more consistent in direction of effect and statistical significance than results reported for ambient $PM_{2.5}$ and preeclampsia, suggesting that a relationship between $PM_{2.5}$ and preeclampsia may only exist when assessing traffic-related $PM_{2.5}$ exposure or sources, rather than total ambient concentrations. However, these studies have used heterogenous measures for assessing traffic based $PM_{2.5}$, and therefore a quantitative meta-analysis is not possible using the current literature. In addition, it is possible that other urban exposures such as urban noise may impact the observed relationships through similar mechanisms as air pollution (Auger et al., 2018; Babisch et al., 2014; Kelishadi et al., 2011; Sears et al., 2018; Yu et al., 2019). Despite the marginal effect found in this study, other meta-analyses have found significant relationships between $PM_{2.5}$ and preeclampsia (Bai et al., 2020; National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020). Additional studies are required to determine the magnitude and significance of this relationship.

4.1. Comparison with previous meta-analyses

Previous studies on the relationships between air pollution and

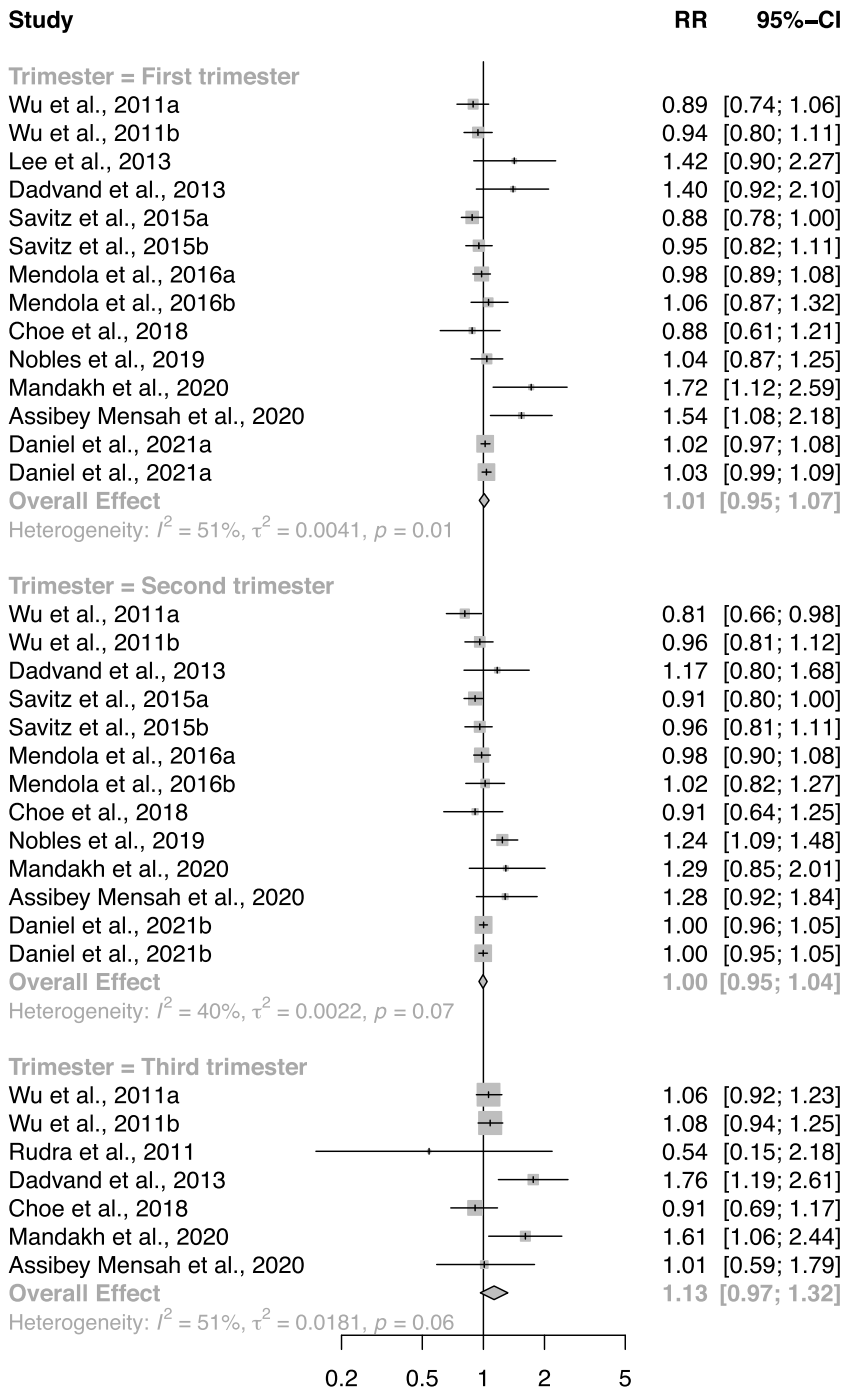

Fig. 5. Subgroup analyses by trimester for relationship between $PM_{2.5}$ and preeclampsia (test for subgroup differences p-value = 0.32). Squares represent relative weights of each study.

preeclampsia have been summarized in three recent systematic reviews and meta-analyses, along with a monograph published by the National Toxicology Program (NTP): Bai et al. (2020): 1.08 [95% CI: 0.97–1.18]; Sun et al., (2020): 1.31 [95% CI: 1.07–1.61]; National Toxicology Program (NTP), 2019: 1.51 [95% CI: 1.04–2.20], and Yu et al. (2020): 1.32 [1.10–1.58]. In contrast to three of these reviews (National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020), we reported a smaller relationship between ambient $PM_{2.5}$ exposure during pregnancy and preeclampsia risk. This is attributable mainly to the inclusion of a traffic based $PM_{2.5}$ study by Wu et al., (2009), instead of a study of the same cohort which used total ambient $PM_{2.5}$ levels (Wu et al., 2011). The mean $PM_{2.5}$ exposure reported in the 2009 study was 1.82 μg/m^3, while the mean exposure reported in the 2011 study, including ambient exposures was 17.3 μg/m^3. Given that the study was conducted in California, where air pollution is typically high, the 2011 study was considered more appropriate to include in an analysis of ambient $PM_{2.5}$ exposure and preeclampsia risk. To further explore our discrepant findings, we conducted a sensitivity analysis where we included Wu et al.'s 2009 paper instead of the 2011 paper. We found this changed the RR from 1.07 (95% CI: 0.99–1.15) to 1.20 (95% CI: 1.01–1.42), which is closer to previously reported estimates (National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2019). Three of the four previous

reviews (Bai et al., 2020; Yu et al., 2020; Sun et al., 2020) included the study by Wu et al. published in 2009, and did not provide rationale for the inclusion of one study over the other.

Other explanations for the discrepant findings among the reviews are likely attributable to differences in inclusion criteria, data extraction, and conversion of measures of effect and 95% CIs to represent changes per 10 μg/m^3. We provide details regarding the studies included and excluded in all reviews, including ours, in Tables A1-A3, as this is likely the most important factor for differences observed across reviews. Although the summary estimate reported in this review is similar to that of Bai et al., studies included in this review were appreciably different from those included by Bai et al., making the similarity in estimates likely due to coincidence rather than a replication of findings (Table A2-A3) (Bai et al., 2020). The review by Bai et al. included the traffic-based $PM_{2.5}$ study by Wu et al. (2009) instead of the total ambient $PM_{2.5}$ study (Wu et al., 2011).

There were also other many other differences between previous review methods and those used in this study. For example, the NTP monograph attempted to focus only on traffic-related air pollution, although they did include estimates of ambient $PM_{2.5}$, and Bai et al. excluded case-control studies from their review. In line with the previous reviews, Egger's weighted linear regression test was non-significant (Bai et al., 2020; National Toxicology Program (NTP), 2019; Sun et al., 2020; Yu et al., 2020), suggesting lack of publication bias for studies on the relationship between $PM_{2.5}$ and preeclampsia.

The small number of studies for sub-group analyses and dose-response meta-analysis was a major limitation of this work. Although the study suggests lack of an overall relationship between $PM_{2.5}$ and preeclampsia, it is possible that differences in the relationship by sub-groups and exposure levels were missed due to underpowered analyses. In addition, we relied on previously conducted systematic reviews to determine eligible studies for inclusion in our meta-analyses, leaving our work open to limitations of systematic searches in previous reviews. However, a new systematic review was deemed unjustified given the recent publishing of four reviews, and it is unlikely that relevant studies were missed when including all studies from previous reviews, as well as an updated search. Finally, we opted to select effect estimates controlling for the largest set of potential confounders where reported. In some instances, this may have included mediators of the relationships of interest, attenuating individual study estimates to the null. Confounders assessed in each study are provided in the Appendix (Table A4).

Our study has several strengths: we provide details regarding inclusion and exclusion decisions, used a novel method to assess dose-response non-linearity, and examined heterogeneity due to sub-group differences by important study characteristics, analyses that were largely ignored in previous reviews.

5. Conclusion

Our work supports a weaker relationship between ambient $PM_{2.5}$ and preeclampsia in comparison to previously published meta-analyses. This is the most comprehensive meta-analysis of the relationship conducted to date, incorporating all studies from these previous systematic reviews as well as more recent studies. Although remaining analyses did not suggest non-linearity in effects, or other sub-group differences, future studies of $PM_{2.5}$ and preeclampsia should consider presenting results for both linear and categorized increases in $PM_{2.5}$ so that reviews may examine non-linearity in meta-analyses with improved study power. Future reviews should also consider source-specific exposures of $PM_{2.5}$.

Author contributions

Priyanka Gogna contributed to study conceptualization, methodology, formal analysis, writing – original draft. **Will D King** contributed to study conceptualization, methodology, writing – review and editing, supervision. **Paul J Villeneuve** contributed to study conceptualization, methodology, writing – review and editing, supervision. **Michael M Borghese** contributed to study conceptualization, methodology, writing – review and editing, supervision.

Ethical approval

This work involved no individual-level human data. This project was approved by the Health Sciences Research Ethics Board at Queen's University (file number: 6031934).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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