1 **Review article and meta-analysis**

2 Long-term impacts of prenatal and infant exposure to fine 3 particulate matter on wheezing and asthma: a systematic review 4 and meta-analysis

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Abstract

Background: This systematic review aimed to summarise epidemiological evidence regarding long-term effects of prenatal and infant fine particulate matter ($PM_{2.5}$) exposure on wheezing and asthma.

Methods: Epidemiological data investigating the associations between ambient $PM_{2.5}$ exposures during prenatal or the first two years of life and wheezing or asthma throughout life was extracted from five databases. All included studies were assessed according to the Critical Appraisal Skills Programme checklists. We performed meta-analyses if ≥2 studies estimated the effects of continuous $PM_{2.5}$.

Results: Nine of 18 eligible studies were suitable for meta-analyses. For prenatal$PM_{2.5}$ exposure and asthma by age 10 (n=4), the overall risk estimate (per 10-unit increase (95% confidence interval) was 1.12 (1.00-1.26). While meta-analysis of prenatal exposure and wheezing by age 4 (n=5) was not possible due to inconsistent exposure and outcome assessments, four studies found strong positive associations with wheeze by age 2. The overall risk of developing asthma (n=5) and wheezing (n=3) by age 8 for infant $PM_{2.5}$ exposure was 1.14 (0.96-1.35) and 1.49 (0.99-2.26), respectively. One large high-quality study reporting risk differences not suitable for meta-analysis demonstrated significant associations between prenatal or infant $PM_{2.5}$ exposure and childhood asthma. High heterogeneity was present among studies of prenatal exposures and asthma, while studies of other associations showed low heterogeneity. There was insufficient evidence about susceptible sub-groups.

Conclusions: The limited and inconsistent evidence is suggestive of an association between early life $PM_{2.5}$ exposure and wheezing/asthma. Large standardised studies are needed to explore the associations and identify vulnerable populations.

Key words: perinatal, particulate matter, wheezing, asthma, meta-analysis

What this study adds: this systematic review provided synthesised results on long-term impacts of prenatal and infant fine particulate matter exposure and development of wheezing or asthma based on the existing evidence. It also highlighted limitations to current research in this rapidly developing field and recommended future epidemiological studies to use standardised designs and evaluate susceptible populations to assist policy makers in improving public health.

1. Introduction

Exposure to fine particulate matter ($PM_{2.5}$) is a well-recognised global public health issue. It has been estimated that mortality from $PM_{2.5}$ exposure increased from approximately 3.5 million in 1990 to 4.2 million in 2015.[1] Globally, the association between $PM_{2.5}$ exposure, wheezing and asthma has been widely studied.[2-4] Short-term (e.g. daily) increases in $PM_{2.5}$ have a well-established association with worsening asthma symptoms and increases in hospital attendance rates,[5] while long-term exposure has been shown to increase the risk of developing asthma.[6] However, few studies have evaluated the long-term impacts of exposure during early life.

The period from *in utero* to the first 2 years of life is a critical window for lung development and growth.[7-8] Increasingly, studies have suggested that exposure to air pollution during this period could increase the risk of developing wheezing and/or asthma in later life. For example, a systematic review has found a significant association between prenatal exposure to particulate matter with an aerodynamic diameter less than 10 μm (PM_{10}) and childhood asthma[9] with *in vivo* laboratory models suggesting that this relationship is causal.[10-11]

However, the identified associations in the literature between $PM_{2.5}$ exposure during this critical period and the long-term risk of wheezing and asthma are inconsistent. For example, an American study suggested that childhood asthma was significantly associated with prenatal $PM_{2.5}$ exposure as estimated by a land use regression (LUR) model (odds ratio (OR): 1.17; 95%CI (confidence interval): 1.04-1.30),[12] while a Canadian study using a similar methodological approach did not observe associations.[13] These inconsistencies might be explained by

differences in $PM_{2.5}$ sources, exposure and outcome measurements, and analytic approaches in different studies, making further analysis necessary to better assess this relationship.

Previous systematic reviews have focused on the effects of either prenatal exposure alone [9] or many years of exposure to traffic-related air pollution.[3, 6] The aim of this systematic review was to identity and summarise the available epidemiological evidence for the association between prenatal or infant (less than 2 years of age) exposure to $PM_{2.5}$ and the subsequent development of wheezing and asthma.

2. Methods

We followed the Cochrane guidelines[14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[15] [See PRISMA 2009 Checklist, Supplemental Digital Content, which provides details of the checklist].

2.1. Search strategy

We initially searched PubMed, Scopus, Web of Science core collection, ProQuest and Cochrane library on 11/05/2016 for scientific articles. We used a combination of free text words found in the title, abstract and key words (Table 1).

We included all respiratory outcomes in the search terms in order to reduce the loss of potentially relevant papers. There was no restriction on publication date. Articles that were not written in English were excluded. We updated the database search and searched the reference lists of all included studies by 4/12/2017.

2.2. Study screening

We screened titles and abstracts of all included papers for potential relevance. After that, full texts of all relevant studies were reviewed based on the following inclusion and exclusion criteria. We included all epidemiological studies which:

1. Were peer-reviewed journal articles, conference proceedings, theses and official reports using a cohort, case-control or cross-sectional design;
2. Evaluated the effects of exposure to $PM_{2.5}$ prenatally or during the first 2 years of life;
3. Assessed the impact of prenatal and infant $PM_{2.5}$ exposure on wheezing and asthma incidence or prevalence $\geq$1 year after the exposure period investigated.

Studies were excluded if they:

1. Were experimental studies, reviews, meeting abstracts, book sections, blogs, newspaper articles, editorials or non-research letters;
2. Only assessed maternal $PM_{2.5}$ exposure before conception or childhood exposure after 2 years of age;
3. Only assessed indoor air pollution, tobacco smoke, or other air pollution exposure metrics;
4. Only assessed other respiratory illnesses or symptoms.
5. Assessed acute effects of $PM_{2.5}$ exposure.

2.3. Data extraction

Data was extracted manually from all eligible studies for information on study design, location, population characteristics, exposure, outcomes, confounding factors and effect estimates with 95%CIs. We contacted the corresponding authors of studies with important data missing.

2.4. Critical appraisal

We examined the quality of all included studies using the Critical Appraisal Skills Programme (CASP) checklists[16-17] [See CASP checklist for cohort study and CASP checklist for case-control study, Supplemental Digital Content, which provides details of these checklists].

2.5. Analysis

We employed random-effects meta-analyses to calculate the weighted effect estimates and 95%CIs for every 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ concentrations. Meta-analysis was conducted if ≥2 studies reporting ORs, RRs or HRs using continuous $PM_{2.5}$ concentrations as an independent variable. Studies reporting ORs, RRs or HRs were combined in a single meta-analysis as this is acceptable for common outcomes with a small effect size[18] and is a well-established approach.[6, 19] All meta-analyses were performed on Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) using the generic inverse variance method. Heterogeneity was assessed using the I^2 statistic and *p* value from the Chi-squared test. Publication bias was visually evaluated using funnel plots. We conducted sensitivity analyses by employing fixed-effects models, excluding case-control studies, and excluding studies estimating exposure using techniques other than the most common approach of LUR. Since one study[20] used both LUR and inverse distance weighted (IDW) approaches to estimate $PM_{2.5}$ exposure, we included LUR in the primary meta-analysis and used IDW in the sensitivity analysis.

3. Results

3.1. Study screening

Our search strategy initially identified 8031 articles (Figure 1). After removing duplicates (n=3326) and conducting the first screening of titles and abstracts (n=4705), we reviewed 111

full texts articles which yielded 13 relevant studies. We added five more articles by further searching for new publications and reference lists of all the included articles. Eighteen studies were included in our final review consisting of 17 peer-reviewed journal articles and 1 Thesis [See eTable 1, Supplemental Digital Content, which provides details].

3.2. Study setting

All 18 studies were published between October 2002 and January 2018. The majority of the studies were conducted in North American and European countries, including 5 in America,[12, 21-24] 3 in Canada,[13, 20, 25] 3 in Poland,[26-28] 2 in Germany,[29-30] 1 in The Netherlands[31] and 1 in the Czech Republic.[32] One study was conducted in Mexico.[33] The remaining two studies were pooled analyses of multi-centre cohorts conducted in Canada, Germany and The Netherlands.[34-35] Sample sizes ranged from 184 to 41,569 and follow-up periods ranged from 2 to 10 years. Most of the studies (n=16) focused on the general population (2 to 21 years of age), except one study of high-risk children (i.e. ≥1 first-degree asthmatic relative or ≥2 first-degree relatives with other IgE-mediated allergic disease)[25] and another on ethnic minorities.[23]

3.3. Study design

Most of the studies were pregnancy or birth cohort studies (n=15) including two pooled analyses of multiple birth cohorts from different locations.[34-35] The remaining three[13, 20, 23] were matched case-control studies in which two were nested within birth cohorts.[13, 20]

3.4. $PM_{2.5}$ sources and measurements

There were 11 studies evaluating outdoor $PM_{2.5}$ from traffic-related sources,[12-13, 20, 22, 24-25, 29-31, 34-35] woodsmoke,[20] industrial points[20] or other sources,[12, 22] while three investigated $PM_{2.5}$ from both outdoor and indoor sources.[26-28] The remaining four studies did not specify the source of ambient $PM_{2.5}$.[21, 23, 32-33]

Various methods were used for estimating prenatal and infant $PM_{2.5}$ exposure. The LUR model was mostly based on Geographic information systems (GIS) [13, 20, 25, 29-31, 34-35] or satellite data.[12, 21-22, 33] Studies estimating prenatal $PM_{2.5}$ exposure[12-13, 20-22, 33] have taken into account participants' residential histories, while studies estimating postnatal exposure[25, 29-31, 34-35] only used birth address. Other studies employed an IDW approach[20, 23] or a dispersion model[24] based on individual's residential histories, personal environmental monitoring samplers (PEMS)[26-28] and data from the central monitoring sites.[32]

3.5. Outcome definition

The majority of the included studies (n=13) relied on questionnaires or interviews to define doctor-diagnosed wheezing and asthma (Table 1). There were four studies defining asthma from medical records as different combinations of physician diagnoses, hospital admissions and asthma-related medication use.[13, 20, 24, 32] One study diagnosed asthma by a blinded paediatric allergist based on the presence of asthmatic symptoms.[25] We included parental reports of doctor diagnosed asthmatic/spastic/obstructive bronchitis as an indication of asthma in two German studies[29-30] due to the relatively low asthma frequency and the strict diagnostic criteria for pre-school asthma.[34]

3.6. Quality assessment

According to the CASP checklists, all the studies were highly [13, 20-22, 24, 32] or moderately qualified[12, 23, 25-31, 33-35] [See eTable 2-3, Supplemental Digital Content, which provides details]. The major concerns for the validity of the studies were potential for information bias (n=13), selection bias (n=10), short follow-up duration (n=9) and not accounting for important confounding factors (n=8) [See eTable 2, eTable 3 and Notes for CASP quality assessment of all included studies, Supplemental Digital Content, which provides details].

3.7. $PM_{2.5}$ exposure and wheezing/asthma

3.7.1 Prenatal $PM_{2.5}$ exposure and asthma

Of the six studies assessing prenatal $PM_{2.5}$ exposure and asthma development, four were included in the meta-analysis,[12-13, 20, 32] while the other two either contained overlapping data[22] or investigated the RDs,[24] respectively. The overall risk of developing childhood asthma for a 10 $\mu g \cdot m^{-3}$ increase in prenatal $PM_{2.5}$ exposure was 1.12 (95%CI: 1.00-1.26), with borderline significance (p=0.050) (Figure 2). We found high heterogeneity among those studies (I^2=73%; p=0.0005). Sensitivity analyses all found similar but non-significant associations between prenatal $PM_{2.5}$ exposure and asthma development(Table 2; see eFigure 1, Supplemental Digital Content, which provides details).

The meta-analyses did not include a recent study using RDs to estimate the effect of prenatal $PM_{2.5}$ exposure on asthma development of nearly 20,000 American children.[24] In this study, the authors found significant positive associations between log-transformed prenatal $PM_{2.5}$ exposure (per 2.7-fold increase) and cumulative asthma incidences from age 2 to age 6 with RDs ranging from 0.015 to 0.035 after adjustment for confounders. Sensitivity analysis of modelling exposure by quintiles also revealed significant associations between prenatal $PM_{2.5}$ exposure and asthma incidence and persistence by age 5. However, modelling $PM_{2.5}$ linearly resulted in positive associations but with no statistical significance [See eTable 4, Supplemental Digital Content, which provides details].

3.7.2 Infant $PM_{2.5}$ exposure and asthma

There were nine studies evaluating the associations between infant $PM_{2.5}$ exposure and asthma. These included one for birth year exposure,[25] four for exposure during the first of life[20, 23-24, 35] and four for exposure during first 2 years of life.[29-31, 34] After excluding four studies either with

repeated data[25, 29, 31] or estimating the effect by RDs,[24] five remained in the meta-analyses.[20, 23, 30, 34-35] Our meta-analyses showed a trend towards a positive association that was not statistically significant (overall OR: 1.14; 95%CI: 0.96-1.35) with low heterogeneity (I^2=0%; p=0.480) (Figure 3). The results were robust to multiple sensitivity analyses (Table 2; see eFigure 2-3, Supplemental Digital content, which provides details).

One study also analysed the outcomes as current asthma or ever asthma plus current wheeze in their regression models,[35] which was not included in the meta-analyses. According to the results of those analyses, infant $PM_{2.5}$ exposure was found to be significantly associated with an increased risk of current asthma of 35% (95%CI: 7%-70%) at age 6 to 8, while ever asthma plus current wheeze did not show statistically significant associations [See eTable 4, Supplemental Digital Content, which provides details].

In the study assessing RDs,[24] significant associations were observed for $PM_{2.5}$ exposure during the first year of life and incident or persistent asthma when modelling exposure as a log-transformed continuous variable and by quintiles. Similar with the results of prenatal $PM_{2.5}$ exposure, modelling the $PM_{2.5}$ as a continuous variable without log-transformation revealed non-significant associations. However, goodness-of-fit analyses suggested that the log-transformed modelling was better than the linear continuous modelling. Other sensitivity analyses all suggested significant associations [See eTable 4, Supplemental Digital Content, which provides details].

3.7.3 Prenatal $PM_{2.5}$ exposure and wheezing

Meta-analysis was not applicable for the five studies of prenatal $PM_{2.5}$ exposure and wheezing since most of the studies categorised $PM_{2.5}$ exposure by median and had different outcome definitions.[21, 26-28]

There was only one study that modelled $PM_{2.5}$ as a continuous variable using regression analyses.[33] The authors evaluated the effect of $PM_{2.5}$ exposure during different trimesters of pregnancy on ever or current wheeze (wheeze in the past year) in 552 4-year-old children. No significant association was observed in any trimester $PM_{2.5}$ exposure and wheezing outcomes. Another study suggested that higher prenatal $PM_{2.5}$ exposure (>11.22 $\mu g \cdot m^{-3}$) was significantly associated with a 102% increase (95%CI: 20%-240%) in the risk of repeated wheezing in children from birth to 2 years old compared with the lower exposure group ($\leq$11.22 $\mu g \cdot m^{-3}$), with consistent results from multiple sensitivity analyses.[21]

The other three studies were from the same project – the Krakow study[26-28] which used PEMS to measure $PM_{2.5}$ exposure during the 2nd trimester of pregnancy. All studies suggested significant associations between prenatal $PM_{2.5}$ exposure and wheezing duration in the first 2 years of life; however, while the association for ages 3 to 4 was also positive, it was not statistically significant [See eTable 4, Supplemental Digital Content, which provides details].

3.7.4 Infant $PM_{2.5}$ exposure and wheezing

Meta-analyses included three of the four studies investigating the association between infant $PM_{2.5}$ and wheezing,[30-31, 35] while the other one containing repeated data was excluded.[29] Infant $PM_{2.5}$ exposure was not associated with wheezing development in either random- or fixed-effects models (overall OR: 1.49; 95%CI: 0.99-2.26) (Figure 4; see eFigure 4, Supplemental Digital Content, which provides details). Low heterogeneity was found in the three studies as indicated by an I^2=0% and a *p* value=0.770. $PM_{2.5}$ was also not significantly associated with current wheeze at age 6 to 8[35] [See eTable 4, Supplemental Digital Content, which provides details].

3.8. Publication bias

Small studies with negative findings have not been published on the associations between prenatal or infant $PM_{2.5}$ exposure and asthma. The distribution was symmetrical in the funnel plot of infant exposure and wheezing, despite the small number of studies included in the meta-analysis [See eFigure 5-7, Supplemental Digital Content, which provides details].

3.9. Outcomes by specific characteristics

There were nine studies including stratified analyses by gender,[12-13, 20, 22-24, 29] heredity,[23-24] maternal stress during pregnancy,[12, 33] race,[24] atopic status[23] and other characteristics including birthweight, gestational length, maternal age, parity, neighbourhood SES[13] and genotype[35] [See eTable 4, Supplemental Digital Content, which provides details].

The differences of effects by gender were inconsistent among the seven studies. To illustrate, two studies suggested larger magnitudes of effects in males compared with females,[12, 22] while the other five suggested stronger effects in females.[13, 20, 23-24, 29] Of those studies, Hsu and colleagues[22] reported significant associations in males exposed to $PM_{2.5}$ during the 12-26th gestational weeks with asthma development, while Pennington and colleagues[24] reported significant associations between infant $PM_{2.5}$ exposure and asthma development in females. Other studies did not show significant results among different genders.

Higher risk was shown for children with a family history of asthma than those without in one study,[23] while the other one[24] only found significantly increased risks of asthma in children of mothers without asthma, but not in children of mothers with asthma.

Stratified analyses by maternal stress during pregnancy revealed a consistently significant and increased risk in children whose mothers were highly stressed during pregnancy compared with those slightly stressed.[12, 33]

Only one study[24] tested for potential effect modification by race or ethnicity and found no statistical differences between groups described as 'white' or 'black'.

Studies that evaluated atopic status[23] and other characteristics including birthweight, maternal age, parity, gestational length and SES[13] did not find any significant associations with asthma. However, evidence of effect modification was seen with birthweight. Children with a birthweight <2500 g were at a higher risk of developing asthma associated with prenatal $PM_{2.5}$ exposure. Children with the GSTP1, rs1138272 or rs1695 minor alleles were more susceptible to developing asthma associated with infant $PM_{2.5}$ exposure.[35]

4. Discussion

Our meta-analyses demonstrated positive associations between prenatal $PM_{2.5}$ exposure and asthma and infant $PM_{2.5}$ exposure, and both wheezing and asthma however there were a limited number of relevant studies and the results were inconsistent. There was high heterogeneity among the studies for prenatal $PM_{2.5}$ exposure and asthma. This might be due to the variability in children's ages, exposure measurement methods, sources of particulate matter, outcome definitions, and adjustment of confounding factors. Studies investigating prenatal $PM_{2.5}$ exposure and subsequent wheezing were not amenable to meta-analysis but consistently reported significant associations, especially in infants (≤2 years).

This is the largest review assessing long-term effects of prenatal and infant $PM_{2.5}$ exposure on subsequent wheezing or asthma. We added three more studies[12, 32-33] to a previous systematic review and meta-analysis of the effects of prenatal exposure to all types of air pollutants including $PM_{2.5}$ on the development of wheezing and asthma.[9] Our results of meta-analyses of the

association between prenatal $PM_{2.5}$ exposure and asthma were similar to this previous review, observing no significant associations and high heterogeneity. In contrast, the other new study not included in meta-analysis reported significantly increased risk of asthma by age 2 to 6 after prenatal exposure to $PM_{2.5}$.[24] However, the evidence was mixed, with more significant associations seen in children followed to school age[12, 24, 32] than preschool age.[20, 24] This phenomenon might be explained by the difficulties in the diagnosis of asthma among young children,[36] leading to the underestimation of physician diagnosed asthma in this population. The significant associations between prenatal $PM_{2.5}$ exposure and wheezing in infants[26-28] rather than in older children[28, 33] could indirectly support this explanation. However, some researchers argue that it is difficult to predict asthma based solely on early life wheezing as less than half of children with episodes of preschool wheezing will have continuing childhood asthma.[37]

For infant $PM_{2.5}$ exposure and the subsequent development of wheezing or asthma, our meta-analyses did not demonstrate an association. However, these studies were of higher risk of bias due to potential for selection bias,[23, 30-31, 34-35] recall bias,[23, 30-31, 34-35] not adjusted for important confounding factors,[20, 35] and a case-control design.[20, 23] In contrast, a recent large, high quality cohort study of nearly 20,000 children revealed positive associations between $PM_{2.5}$ exposure during the first year of life and asthma incidence by age 6, despite not adjusting for important confounders.[24] This result was robust to different asthma definitions but sensitive to $PM_{2.5}$ modelling decisions and covariate controls. Overall, the small number of studies identified in this systematic review limited our confidence in conclusively suggesting the presence or absence of associations. Studies with a larger sample size, a standardised exposure estimate method, more accurate outcome assessment approaches and greater statistical power are needed to further

explore the long-term effects of prenatal and infant $PM_{2.5}$ exposure on asthma or wheeze development.

Our review also highlights the limited evidence of susceptible populations to prenatal and infant $PM_{2.5}$ exposure. Children whose mothers were exposed to negative life events during pregnancy were more likely to develop wheezing or asthma after prenatal and infant $PM_{2.5}$ exposure than those not exposed. The different effects of $PM_{2.5}$ exposure by gender and heredity were inconsistent between studies. There was insufficient evidence to suggest that race, low birth weight and specific genotypes could increase the risk of wheezing or asthma development after $PM_{2.5}$ exposure, while the effects of atopic status, gestational length, maternal age, parity and SES require further investigation.

The main strength of our systematic review was the comprehensive search strategy and reproducible evaluation of current evidence. Our findings provide a timely contribution to the rapidly developing field, which could highlight limitations and guide future studies. However, some limitations should also be acknowledged. Firstly, evidence of prenatal and infant $PM_{2.5}$ exposure and wheezing or asthma is still limited. In addition, publication bias might be present in studies evaluating early life $PM_{2.5}$ exposure and asthma. Therefore, any conclusions should be made with caution and confirmed by further investigations. Secondly, high variability was found between studies in study design, exposure estimating methods, outcome assessment approaches, participants' ages at assessment and adjustment of confounders, especially in those evaluating prenatal $PM_{2.5}$ exposure and asthma. Future syntheses of evidence in this area will benefit from more studies using standardised designs and methods. In addition, diagnosis of asthma in young children is difficult and outcome misclassification is inevitable in this population. Finally, the major source of $PM_{2.5}$ in this systematic review was traffic, with scarce evidence regarding the

long-term respiratory effects of early life $PM_{2.5}$ exposure from other sources such as wildfire smoke, which is an increasing global concern due to climate change.[38-39] More research on $PM_{2.5}$ from other sources is needed to guide public health responses.

5. Conclusions

Prenatal and infant $PM_{2.5}$ exposure was not clearly associated with subsequent development of wheezing or asthma in our review of the literature. The strongest evidence was for an association between prenatal $PM_{2.5}$ exposure and wheezing in infants, while *in-utero* exposure and asthma had a borderline positive overall effect estimate. However, evidence was insufficient and mixed, indicated by a small number of studies included in the meta-analyses and inconsistent results. Further research is necessary to explore the associations using harmonised exposure methods and appropriate statistical analyses controlling for important covariates. Furthermore, studies of susceptible populations and other sources of $PM_{2.5}$ are needed to help policy makers improving public health.

Appendix

Supplemental Digital Content: this supplementary material includes the PRISMA 2009 checklist, information on CASP quality assessment, and figures/tables listed below.

eFigure 1. Sensitivity analysis of the association between prenatal $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and asthma

eFigure 2. Fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and asthma

eFigure 3. Sensitivity analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{3}$) and asthma

eFigure 4. Fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and wheezing

eFigure 5. Funnel plot – fixed-effects meta-analysis of the association between prenatal $PM_{2.5}$ exposure and asthma

eFigure 6. Funnel plot – fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure and asthma

eFigure 7. Funnel plot-fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure and wheezing

eTable 1. Summary of studies included in the systematic review

eTable 2. Risk of bias assessment for cohort studies according to the CASP checklist

eTable 3. Risk of bias assessment for case-control studies according to the CASP checklist

eTable 4. Original risk estimates of the 18 studies investigating prenatal and infant $PM_{2.5}$ exposure and wheezing/asthma development

406 **Table 1.** Items for database search

Population	Connecting word	Exposure	Connecting word	Outcome
perinatal	AND	"air pollution"	AND	respirat*
post-natal		"air pollutant*"		lung
prenatal		particle*		pulmon*
pre-natal		"particulate matter*"		bronchi*
maternal				"air way"
pregnan*				airway
gestation				asthma
conception				cough
fetus*				wheeze
foetus*				wheezing
fetal				
newborn*				
"new born*"				
infant*				

407 **Notes:** Asterisk represents any combination of letters; double quotation marks represent that the two words should
408 not be broken apart.

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Table 2. Prenatal and infant $PM_{2.5}$ exposure (per 10 μg·m^{-3} increase) on wheezing/asthma from the sensitivity meta-analyses

	Sensitivity analysis 1: fixed-effects OR (95%CI); I^2 (p^* value)	**Sensitivity analysis 2:** excluding case-control studies random-effects OR (95%CI); I^2 (p^* value)	**Sensitivity analysis 3:** excluding studies with other exposure estimates approaches except LUR random-effects OR (95%CI); I^2 (p^* value)
Prenatal $PM_{2.5}$ & asthma	**N.A.**	1.17 (0.99 to 1.37); 78% (0.001)	1.16 (0.91 to 1.48); 77% (0.004)
Infant $PM_{2.5}$ & asthma	1.14 (0.96 to 1.35); 0% (0.480)	1.27 (0.82 to 1.98); 22% (0.280)	1.16 (0.92 to 1.44); 9% (0.360)
Infant $PM_{2.5}$ & wheezing	1.49 (0.99 to 2.26); 0% (0.770)	N.A.	N.A.

Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval; LUR, land use regression; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; N.A., not applicable. Significant associations are shown in bold. *, *p*-value refers to the test of heterogeneity.

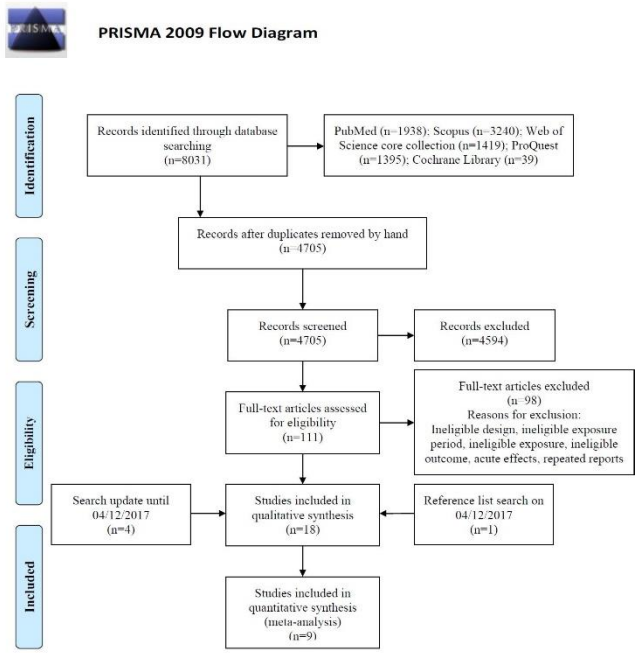

Figure 1. PRISMA flow diagram describing the database search and study screening process

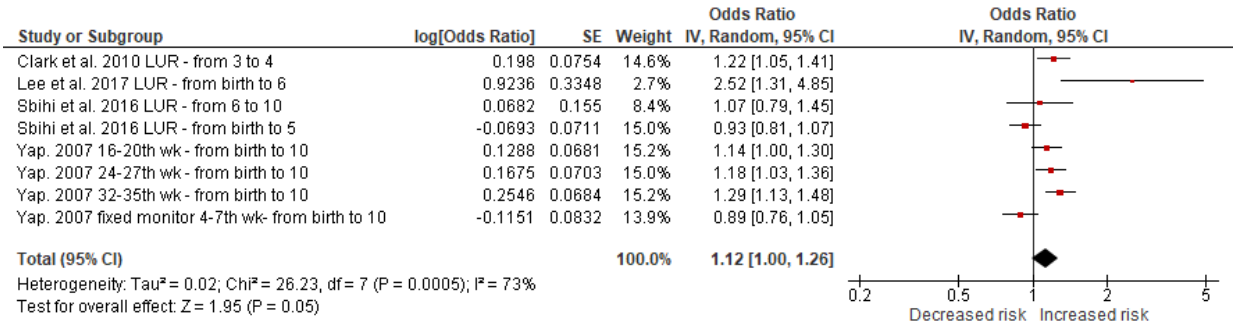

Figure 2. Random-effects meta-analysis of the association between prenatal $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and asthma

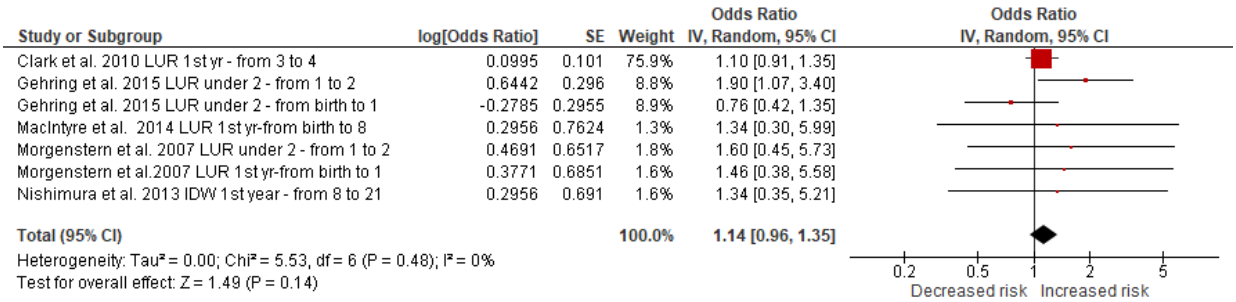

Figure 3. Random-effects meta-analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and asthma

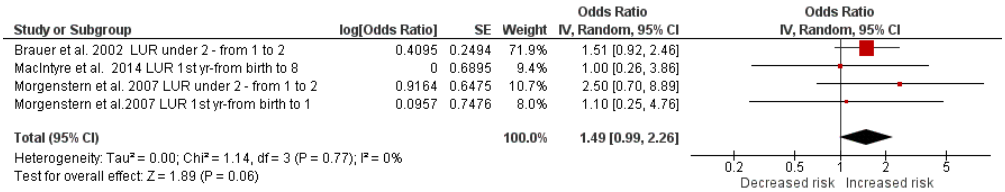

Figure 4. Random-effects meta-analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and wheezing

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