Supplemental Digital Content

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

Jingyi Shao, Amanda J. Wheeler, Graeme R. Zosky, Fay H. Johnston

Supplemental Digital Content

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Supplemental Digital Content–PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N.A.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6 & Supplemental Digital Content
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias,	6

studies		selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8, eTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, eTable 2-3, Supplemental Digital Content
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2-4, eTable 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11, Figure 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12, eFigure 5-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item	9-11, Table 2, eFigure 1-

		16]).	4
15-DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-16, Supplemental Digital Content
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

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CASP checklist for cohort study

Section/Topic	#	Checklist item
Section A. Are the results of the study valid?		
Screening Questions		
	1	Did the study address a clearly focused issue?
Selection bias	2	Was the cohort recruited in an acceptable way?
Detailed Questions		
Measurement of classification bias	3	Was the exposure accurately measured to minimise bias?
	4	Was the outcome accurately measured to minimise bias?
Confounding factors	5a	Have the authors identified all important confounding factors?
	5b	Have they taken account of the confounding factors in the design and/or analysis?
Completion and length of follow-up	6a	Was the follow up of the subjects complete enough?
	6b	Was the follow up of subjects long enough?
Section B. What are the results?		
	7	What are the results of this study?
	8	How precise are the results?
	9	Do you believe the results?
Section C. Will the results help locally?		
	10	Can the results be applied to the local population?
	11	Do the results of this study fit with other available evidence?
	12	What are the implications of this study for practice?

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CASP checklist for case-control study

Section/Topic	#	Checklist item
Section A. Are the results of the study valid?		
Screening Questions		
	1	Did the study address a clearly focused issue?
	2	Did the authors use an appropriate method to answer their question?
Detailed Questions		
Selection bias	3	Were the cases recruited in an acceptable way?
	4	Were the controls selected in an acceptable way?
Measurement, recall or classification bias	5	Was the exposure accurately measured to minimise bias?
Confounding factors	6a	What confounding factors have the authors accounted for?
	6b	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?
Section B. What are the results?		
	7	What are the results of this study?
	8	How precise are the results? How precise is the estimate of risk?
	9	Do you believe the results?
Section C. Will the results help locally?		
	10	Can the results be applied to the local population?
	11	Do the results of this study fit with other available evidence?

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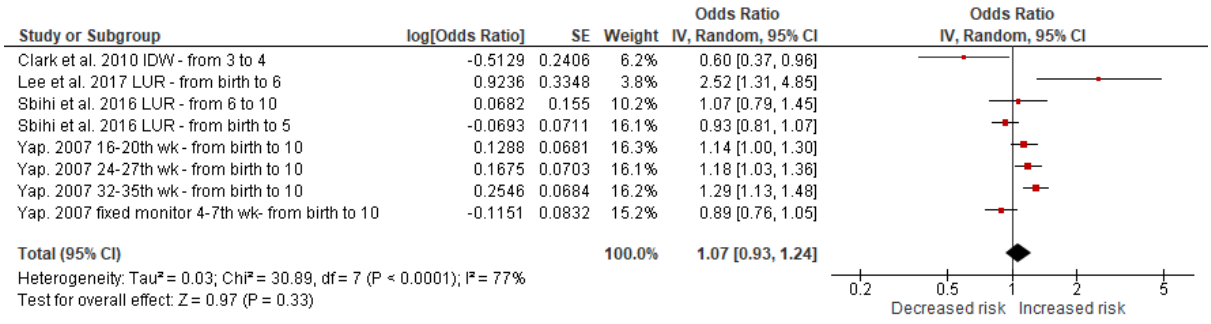

eFigure 1. Sensitivity analysis of the association between prenatal $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and asthma

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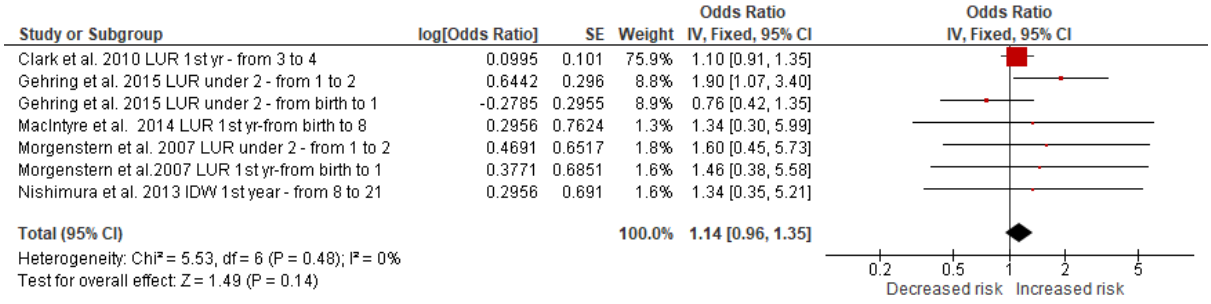

eFigure 2. Fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and asthma

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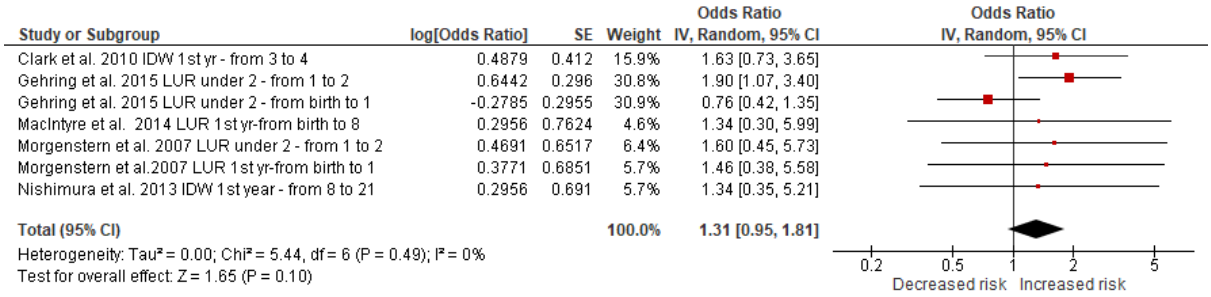

eFigure 3. Sensitivity analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^3$) and asthma

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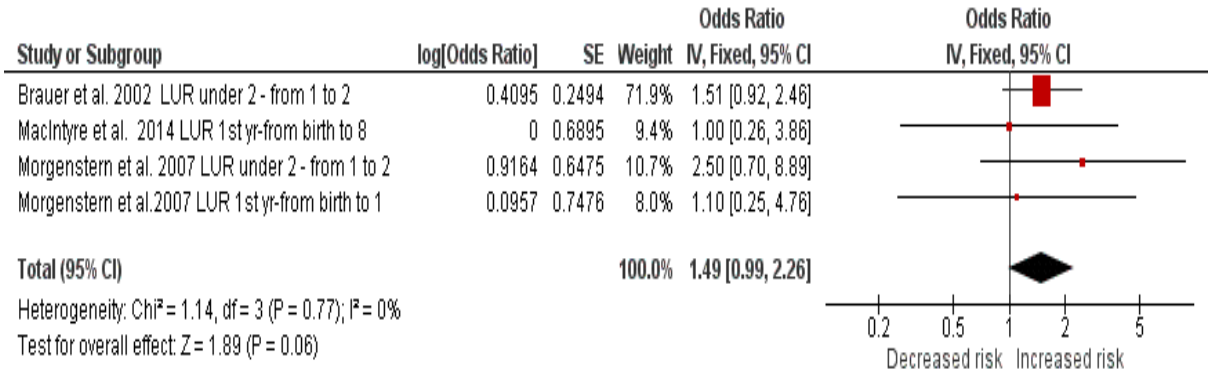

eFigure 4. Fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$) and wheezing

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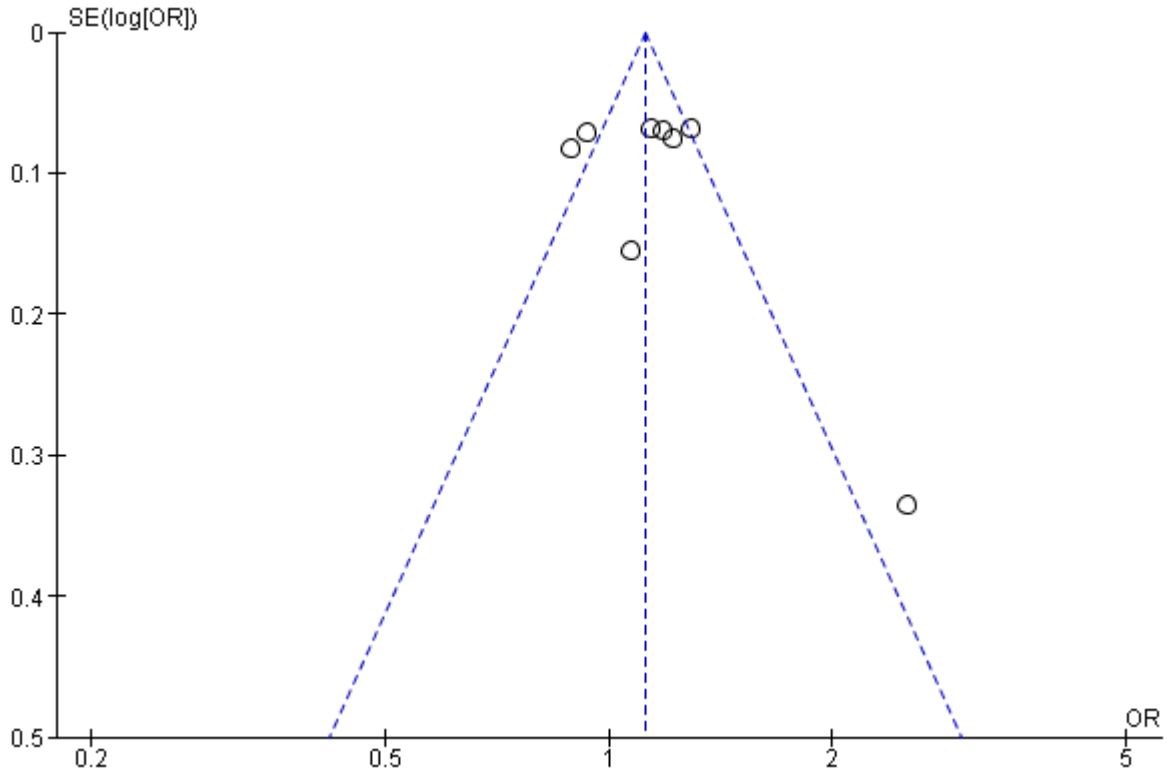

eFigure 5. Funnel plot – fixed-effects meta-analysis of the association between prenatal $PM_{2.5}$ exposure and asthma

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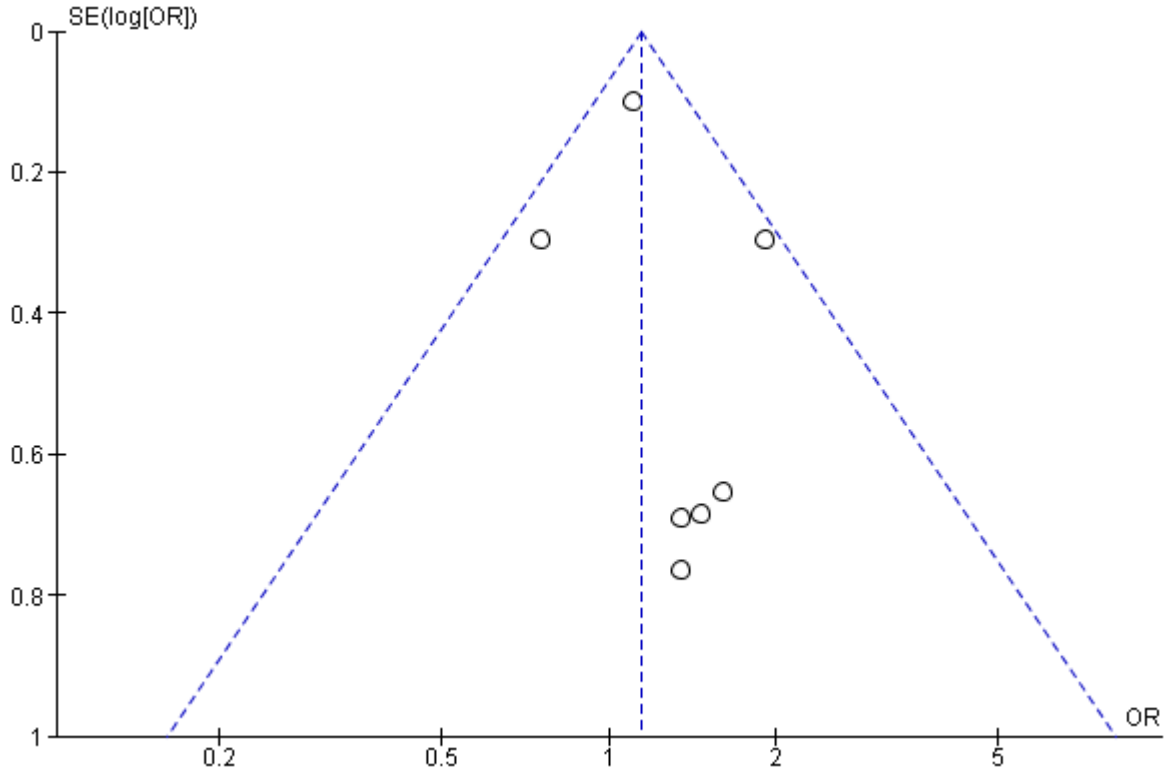
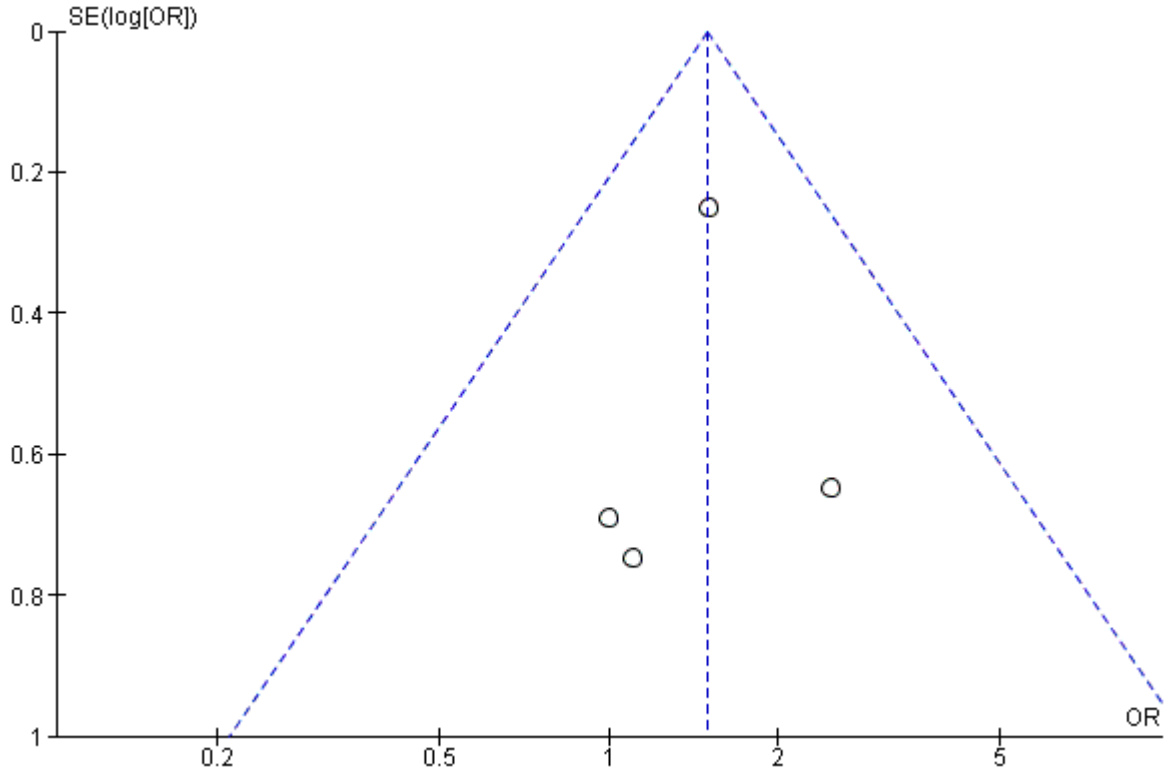


eFigure 6. Funnel plot – fixed-effects meta-analysis of the association between infant $PM_{2.5}$ exposure and asthma

Supplemental Digital Content



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

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eTable 1. Summary of studies included in the systematic review

Study reference	**Study design**	**Study location**	**Sample size**	**$PM_{2.5}$ source; exposure estimate**	**Exposure period**	**$PM_{2.5}$ levels ($\mu g \cdot m^{-3}$)**	**Outcome definition**	**No. (%) of cases**	**Ages for outcome (years)**	**Confounding factors**
Lee et al.[4] (Study 12)	Cohort (ACCESS)	Boston, USA	736	Traffic and other source; satellite-based LUR model according to residential history	Prenatal	Median [IQR]: 11.2 [10.2-11.9]	Maternal report of doctor-diagnosed asthma	110 (14.9%)	0-6	Gender, race/ethnicity, maternal age, prepregnancy obesity, maternal education, maternal prenatal and postnatal smoking
Sbihi et al.[5] (Study 13)	Nested case-control	Vancouver, Canada	6,948 preschool cases and 34,621 controls or	Traffic; GIS-based LUR model according to residential	Prenatal	Mean±SD: Preschool age: 4.09±1.6 for cases,	Asthma: ≥2 primary care physician diagnoses/≥1 hospital admission in a rolling 12 months according to ICD-9 code	Preshool age: 6948 (16.7%); school	0-5; 6-10	Gender, birth month and year, birthweight, gestational age, parity, breastfeeding, maternal education, area level income

			1,711 school cases and 8,577 controls from 68,195 births	history		4.06±1.7 for controls; school age: 4.1±1.6 for cases, 4.0±0.7 for controls	493 and ICD-10 J45 from medical records	age: 1711 (16.6%)		
Clark et al.[6] (Study 20)	Nested case-control	Southwestern British Columbia, Canada	LUR: 3,254 cases and 16,270 controls; IDW: 3,355 cases and 16,775 controls from	Traffic, woodsmoke and industry; GIS-based LUR model for traffic-related and woodsmoke sources & IDW approach for industrial	Prenatal; first year of life	Mean±SD: Prenatal: 4.8±2.5 for cases, 4.7±2.5 for controls (LUR), 4.7±1.2 for cases and controls (IDW); first	Asthma: ≥2 primary care physician diagnoses in a rolling 12 months/≥1 hospital admission for asthma according to ICD-9 code 493 from medical records	LUR: 3254 (16.7%); IDW: 3355 (16.7%)	3-4	Age, gender, birthweight, gestational age, parity, breastfeeding, maternal education and neighbourhood level income in the final model; native status, maternal age and maternal smoking were also considered

			37,401 births	source according to residential history		year of life: 4.6±2.4 for cases, 4.5±2.5 for controls (LUR), 5.6±0.6 for cases and controls (IDW)				
Chiu et al.[7] (Study 21)	Cohort (ACCESS)	Boston, USA	708	Outdoor source (not specified); satellite-based LUR model according to residential history	Prenatal	Median [IQR]: 11.2 [10.3-11.9]	Maternal reported repeated wheeze: ≥2 episodes	87 (12.3%)	0-2	Gender, race/ethnicity, season of birth, maternal education, maternal atopy, cockroach exposure, prenatal community violence
Hsu et al.[8]	Cohort	Boston,	736	Traffic and	Prenatal	Median	Maternal report of	110	0-6	Gender, race/ethnicity,

(Study 22)	(ACCESS)	USA		other source; satellite-based LUR model according to residential history		[IQR]: 11.2 [10.2-11.8]	doctor-diagnosed asthma	(14.9%)		maternal age, prepregnancy obesity, maternal education, maternal prenatal and postnatal smoking, prenatal stress
Nishimura et al.[9] (Study 23)	Case-control (GALA II and SAGE II)	Chicago, Bronx, Houston, San Francisco Bay Area, and Puerto Rico, USA	514 cases and 434 controls	Outdoor source (not specified); IDW approach	First year of life	Mean±SD: 11.8±3.6	Parental report of asthma: doctor-diagnosed asthma plus ≥2 symptoms of coughing, wheezing or shortness of breath in the 2 years before recruitment	514 (54.2%)	8-21	Age, ethnicity, region, SES and income in final model; maternal smoking during pregnancy, ETS exposure during the first 2 years of life, maternal language of preference were also considered
Pennington et al.[10] (Study 24)	Cohort (KAPPA)	Atlanta, USA	19,951 for prenatal exposure; 23,100 for first year	Traffic; research Line-source dispersion model for	Prenatal; first year of life	Median: prenatal: 1.5; first year of life: 1.4	Asthma: ≥1 asthma diagnosis according to ICD-9 493.XX and 1 asthma-related medication dispensing	Prenatal: 1854 (32%); first year of life:	1-6	Gender, race, city region, birth year, maternal asthma, neighbourhood SES in final model; ethnicity, maternal age, marital status, and

			of life exposure	near-surface releases according to residential history			(steroid/non-steroid asthma controllers and relievers) from medical records	2149 (32%)		parental education were also considered
Carlsten et al.[11] (Study 25)	Cohort (CAPPS)	Vancouver, Canada	184 high-risk children*	Traffic; GIS-based LUR model according to birth address	During the year of birth	Mean±SD: 5.6±2.6	Asthma diagnosed by a blinded paediatric allergist: ≥2 distinct cough (each ≥2 weeks), ≥2 distinct wheeze (each ≥1 week), and ≥1 of the following: nocturnal cough (≥once a week) without a cold, hyperpnoea-induced cough/wheeze, or response to β-agonist and/or anti-inflammatory drugs	23 (12.5%)	7	Gender, ethnicity, intervention status, maternal education, family history of asthma, atopy at 1 year

Jedrychowski et al.[12] (Study 26)	Cohort (Krakow study)	Krakow, Poland	465	Indoor and outdoor sources (not specified); PEMS	Prenatal: *2nd trimester*	Mean [range]: 36.1 [10.3-294.9]	Maternal reported duration of wheezing/whistling of the chest irrespective of respiratory infection	125 (26.9%)	0-2	Gender, gestational age, parity, fish consumption during pregnancy, maternal atopy, mold at home and postnatal ETS exposure in the final model; breastfeeding and maternal education were also considered
Jedrychowski et al.[13] (Study 27)	Cohort (Krakow study)	Krakow, Poland	465	Indoor and outdoor sources (not specified); PEMS	Prenatal: *2nd trimester*	Mean [range]: 36.1 [10.3-294.9]	Maternal reported duration of wheezing/whistling of the chest irrespective of respiratory infection	125 (26.9%)	0-2	Gender, parity, maternal education, maternal atopy, postnatal ETS exposure, mold at home
Jedrychowski et al.[14] (Study 28)	Cohort (Krakow study)	Krakow, Poland	339	Indoor and outdoor sources (not specified); PEMS	Prenatal: *2nd trimester*	Median [range]: 35.4 [10.3-294.9]	Maternal reported duration of wheezing/whistling in the chest irrespective of respiratory infection	139 (41.0%)	0-4	Gender, parity, maternal age, maternal education, maternal atopy, cord blood polycyclic aromatic hydrocarbon - adducts, dampness/mold at home, presence of wheeze

										during first 2 years (only in the 3-4 years model) in the final model; prenatal ETS exposure was also considered
Gehring et al.[15] (Study 29)	2 cohorts: GINI and LISA	Munich, Germany	1,517 for wheezing; 1,510 for asthma	Traffic; GIS-based LUR model according to birth address	First 2 years of life	Mean [range]: 13.4 [11.9-21.9]	Parental report of wheezing and doctor-diagnosed asthmatic/spastic/obstructive bronchitis	Wheezing: age 1: 258 (15.0%); age 2: 416 (25.6%); asthma: age 1: 196 (11.3%). Age 2: 303 (8.8%)	0-2	Gender, study arm, parity, maternal education, parental atopy, smoking at home, gas cooking, dampness/mold/pets at home
Morgenstern	2 cohorts:	Munich	2,882 for	Traffic;	First 2	Mean	Parental report of	Wheezin	0-2	Gender, parity, maternal

et al.[16] (Study 30)	GINI and LISA	metropolitan area, Germany	wheezing; 2,861 for asthma	GIS-based LUR model according to birth address	years of life	[range]: 12.8 [6.8-15.3]	wheezing and doctor-diagnosed asthmatic/spastic/obstructive bronchitis	g: age 1: 471 (15.5%); age 2: 746 (25.9%); asthma: age 1: 356 (11.6%). Age 2: 555 (19.4%)		education, parental atopy, ETS at home, gas cooking, dampness/mold/pets at home
Brauer et al.[17] (Study 31)	Cohort (PIAMA)	Northern, western and central parts of The Netherlands	2,989 for asthma; 2,991 for wheezing	Traffic; GIS-based LUR model according to birth address	First 2 years of life	Mean [range]: 16.9 [13.5-25.2]	Parental report of doctor-diagnosed asthma and wheezing/whistling of the chest in the past 12 months	Asthma: 176 (4.8%); wheezing: 697 (18.8%)	1-2	Gender, ethnicity, study arm, maternal age, parity, breastfeeding, parental education, parental allergic status, maternal smoking during pregnancy, smoking at

										home, mattress cover, gas cooking, unvented gas water heater, any mold/pets at home
Yap[18] (Study 32)	Cohort (the Czech Republic project)	Teplice and Prachatice, Czech Republic	1,133	Outdoor source (not specified); fixed central monitoring sites	Prenatal: 4-7th, 16-20th, 24-27th, and 32-35th weeks of gestation	N.A.	Asthma: first diagnosis of asthma according to ICD-10 J45 from pediatric records	N.A.	0-10	District, birth season, parental allergy in the final model; maternal smoking during pregnancy was also considered
Rosa et al.[19] (Study 33)	Cohort (PROGRESS)	Mexico City, Mexico	552	Outdoor source (not specified); satellite-based LUR model according to residential history	Prenatal	Median [IQR]: 1st trimester: 22.0 [18.9-25.7]; 2nd trimester: 21.1 [18.8-25.6], 3rd trimester:	Caregivers' report of ever wheeze and current wheeze (wheezing/whistling of the chest in the past 12 months)	Ever wheeze: 136 (24.6%); current wheeze: 66 (12.0%)	0-4	Gender, maternal age, maternal asthma, prenatal/postnatal ETS exposure, $PM_{2.5}$ exposure during other trimesters and 1 year in the final model; maternal stress and SES were also considered

						22.5 [19.0-27.3]				
Gehring et al.[20] (Study 34)	Pooled analysis of 4 cohorts (MeDALL study): BAMSE, GINIplus, LISAplus, PIAMA	Stockholm, Sweden; Munich and Wesel area, Germany; northern, western and central part of The Netherlands	14,126	Outdoor source (mainly traffic); GIS-based LUR model according to birth address (BAMSE: dispersion model)	First 2 years of life	Mean±SD: 7.8±1.2 for BAMSE; 17.4±0.7 for GINI/LISA North; 13.4±1.0 for GINI/LISA South; 16.4±0.7 for PIAMA	Parental report of asthma: ≥2 of the following: doctor-diagnosed asthma, wheezing/whistling of the chest in the past 12 months or prescribed asthma medication during the past 12 months	N.A.	0-2	Native nationality, cohort, parity, breastfeeding, parental education, parental asthma or hay fever, maternal smoking during pregnancy, parental smoking at home, gas cooking, dampness/mold/pets at home, daycare attendance and municipality (BAMSE) in final model; gender and SES were also considered
MacIntyre et al.[21] (Study 35)	Pooled analysis of 4 cohorts (TAG study): LISA,	Munich, Germany; northern, western and central parts of The	2,755 (CAPPS only included high-risk children)	Traffic; GIS-based LUR model according to birth address	First year of life	Mean±SD: 15.2±3.4	Parental report of doctor-diagnosed asthma and wheeze symptoms; asthma was also confirmed by a pediatric allergist in CAPPS	N.A.	0-8	Gender, study, intervention status, city, birthweight, maternal age, parental allergy, maternal smoking during pregnancy, ETS at home, NO2 exposure during first year of

	GINI, PIAMA, CAPPS	Netherlands; Vancouver, Canada								life

Abbreviations: PIAMA, the Prevention and Incidence of Asthma and Mite Allergy study; GIS, geographic information system; LUR, land use regression; CAPPS, the Canadian Asthma Primary Prevention study; SD, standard deviation; ACCESS, the Asthma Coalition on Community, Environment, and Social Stress project; IQR, interquartile range; IDW, inverse distance weighted; ICD, International Classification of Disease; GINI, German Infant Nutrition Intervention Programme; LISA; Influences of Lifestyle Related Factors on the Immune System and Development of Allergies in Children; MeDALL, Mechanisms of the Development of Allergy project; BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; GINIplus, German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development; LISAplus, Life style Immune System Allergy plus air pollution and genetics; N.A., not applicable; SES, socioeconomic status; PEMS, personal environmental monitoring sampler; ETS, environmental tobacco smoke; TAG, the Traffic, Asthma and Genetics study; NO_2, nitrogen dioxide; GALA II, the Genes-environments and Admixture in Latino Americans; SAGE II, the Study of African Americans, Asthma, Genes and Environments; KAPPA, the Kaiser Air Pollution and Pediatric Asthma study; PROGESS, the Programming Research in Obesity, Growth, Environment and Social Stressors study; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 µm. *, Having ≥ 1 first-degree asthmatic relative or ≥2 first-degree relatives with other IgE-mediated allergic disease

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

Study reference	1	2	3	4	5	6a	6b	9	10	11	Notes	Quality
Lee[4] (Study 12)	Yes	No-low recruitment rate (78.1%); although not significant, non-participants were slightly less likely to be ethnic minorities or to have a low education level and slightly more likely to report a low income level than the participants	Yes	No-maternal reported outcomes	No-not adjusted for heredity	Yes	Yes-from birth to 6	Yes	No-see comments in Column 3	Yes	Maternal reported outcome: reporting/recall bias; not adjusted for heredity; not accounted for other pollutants; not generalisable to the overall US population	Moderate
Chiu[7] (Study 21)	Yes	Yes	Yes	No-maternal reported outcomes	No-not adjusted for ETS exposure	Yes	No-from birth to 2	Yes	Yes	Yes	Not adjusted for ETS exposure; maternal reported outcome: reporting/recall bias; small sample size	High
Hsu[8] (Study 22)	Yes	No-low recruitment rate (78.1%);although not significant, non-	Yes	No-maternal reported	Yes	Yes	Yes-from birth to 6	Yes	No-see comments in Column 3	Yes	Maternal reported outcomes: recall/reporting bias; not generalisable to the overall US	High

		participants were slightly less likely to be ethnic minorities or to have a low education level and slightly more likely to report a low income level than the participants		outcomes							population	
Pennington[10] (Study 24)	Yes	Yes	Yes	Yes	No-not adjusted for ETS exposure	Yes	Yes-from birth to 6	Yes	Yes	Yes	Not adjusted for ETS; lack of detailed data on individual-level SES, high correlation between prenatal and postnatal exposure: unable to determine the relative importance of exposure during different periods; outcome misclassification in early life asthma; KPGA population: urban population with high asthma rates, large African American	High

											population, and high SES: not generalisable to distinctly different populations	
Carlsten[11] (Study 25)	Yes	No-a small high-risk population*	Yes	Yes	No-not adjusted for ETS exposure	No-37% loss of follow-up	Yes-from birth to 7	Yes	No-a small high-risk group	Yes	A small high risk group; not adjusted for ETS exposure; modest sample size: limiting the precision in effect estimates; extrapolation of the LUR based estimates over time	Moderate
Jedrychowski[12] (Study 26)	Yes	Can't tell	Yes	No-maternal reported outcomes	Yes	Yes	No-from birth to 2	Yes	Can't tell	Yes	Non-smoking mothers; unable to distinguish the effect of prenatal exposure from that of the postnatal exposure; maternal reported outcomes: reporting/recall bias	Moderate
Jedrychowski[13] (Study 27)	Yes	Can't tell	Yes	No-maternal reported outcomes	Yes	Yes	No-from birth to 2	Yes	Can't tell	Yes	Non-smoking mothers; unable to distinguish the effect of prenatal exposure from that of the postnatal exposure; maternal reported outcomes: reporting/recall bias	Moderate
Jedrychowski[14]	Yes	Can't tell	Yes	No-	Yes	No-33%	No-from	Yes	Can't tell	Yes	Non-smoking mothers; unable to	Moderate

(Study 28)				maternal reported outcomes		loss to follow-up & incomplete data	birth to 4				distinguish effect of prenatal exposure from that of the postnatal exposure; maternal reported outcomes: reporting/recall bias	
Gehring[15] (Study 29)	Yes	No-a higher rate of participants with an atopic and a well-educated (>10 years) parent compared with the original cohort reported by Fuertes et al.[22]	Yes	No-parental reported outcomes	Yes	Yes	No-from birth to 2	Yes	No-likely to exclude children with non-atopic and less-educated parents	Yes	Unable to distinguish between long-term and short-term effects: exposure and health data collected on an annual basis instead of a daily basis; questionnaire data: recall/reporting bias; excluding preterm births and low birth weight infants in LISA might bias the results towards the null; young age for accurate diagnosis; short follow-up duration	Moderate
Morgenstern[16] (Study 30)	Yes	No- a higher rate of participants with an atopic and a well-	Yes	No-Parental reported	Yes	Yes	No-from birth to 2	Yes	No-likely to exclude children with	Yes	No validated exposure measurements for suburbs; questionnaire data: reporting/recall	Moderate

		educated (>10 years) parent compared with the original cohort [22]		outcomes					non-atopic and less-educated parents		bias; high rates of well-educated and non-atopic parents; excluding preterm birth/low birth weight infants in LISA may bias the results towards the null; young age for accurate diagnosis; short follow-up duration	
Brauer[17] (Study 31)	Yes	No-low recruitment rate (53%) according to Koopman et al.[23]	Yes	No-parental reported outcomes	Yes	Yes	No-from birth to 2	Yes	Can't tell	Yes	Questionnaire data: recall/reporting bias; misclassification of asthma for infants and very young children; short follow-up duration	Moderate
Yap[18] (Study 32)	Yes	No-low recruitment rate (17%); more full term, normal birth weight children sampled from the POS	Yes	Yes	No-not adjusted for SES	Yes	Yes-from birth to 10	Yes	No-more full term, normal birth weight children sampled from the POS	Yes	More full term, normal birth weight children than the local population; not adjusted for SES; exposure measurements relied on daily average pollution at one central location for each districts: misclassification for individuals	High
Rosa[19]	Yes	Can't tell	Yes	No-	Yes	No-32%	no-from	Yes	Can't tell	Yes	Caregiver reported outcomes:	Moderate

(Study 33)				caregiver reported outcomes		loss to follow-up & incomplete data	birth to 4				reporting/recall bias	
Gehring[20] (Study 34)	Yes	No-BAMSE: low recruitment rate (75%); less smoking parents in the cohorts than the local population according to Wickman et al.[24]; GINIplus and LISAplus: a higher rate of participants with an atopic and well-educated parent compared with the original cohort [22]; PIAMA: 53% recruitment rate;	Yes	No-parental reported outcomes	Yes	Yes	No-from birth to 2 (further follow-up data were not included in this review)	Yes	No-see comments in Column 3	Yes	Questionnaire data: reporting/recall bias; not generalisable to local population: children with well-educated parents were over-represented; exposure models based on air pollution measurement campaigns from 2008-2010 to assess exposure for the entire duration of follow-up & based on birth addresses without accounting for locations other than home or time-activity patterns and long term trends	Moderate

		including more well-educated native-speakers compared with general population in The Netherlands [25]										
MacIntyre[21] (Study 35)	Yes	No-fewer infants with low birth weight, more older mothers, more atopic parents and fewer mothers smoking during pregnancy compared with the total recruited population for each cohort; CAPPS only included a small high-risk population[a]	Yes	No-parental reported outcomes, except CAPPS being confirmed by pediatric allergists	No-not adjusted for SES	No-46% loss to follow-up & incomplete data	Yes-from birth to 8	Yes	No-fewer infants with low birth weight, more older mothers, more atopic parents and fewer mothers smoking during pregnancy in the cohorts	Yes	Not adjusted for SES; fewer infants with low birth weight, more older mothers, more atopic parents and fewer mothers smoking during pregnancy in the cohort compared with total recruited population for each cohort: selection bias; parental reported outcomes: recall/reporting bias	Moderate

									than in the local population			

Abbreviations: ETS, environmental tobacco smoke; LUR, land use regression; LISA, Influences of Lifestyle Related Factors on the Immune System and Development of Allergies in Children; BMASE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; GINI, German Infant Nutrition Intervention Programme; PIAMA, the Prevention and Incidence of Asthma and Mite Allergy study; CAPPS, the Canadian Asthma Primary Prevention study; SES, socioeconomic status; KPGA, Kaiser Permanente Georgia; POS, the Pregnancy Outcome Study. *, Having ≥ 1 first-degree asthmatic relative or ≥2 first-degree relatives with other IgE-mediated allergic disease

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

Study reference	1	2	3	4	5	6	9	10	11	Notes	Quality
Sbihi[5] (Study 13)	Yes	Yes-cohort better	Yes	Yes	Yes	No-not adjusted for heredity and ETS exposure	Yes	Yes	Yes	Administrative data were not collected for research purposes and lacked individual-level information (e.g. SES measures); exposure misclassification: exposures in microenvironments other than the homes during pregnancy were not considered; no formal comparison of pregnancy and post-natal exposures was conducted in the absence of linked residential histories throughout the follow-up period; not adjusted for heredity	High

										and ETS exposure	
Clark[6] (Study 20)	Yes	Yes-cohort better	Yes	Yes	Yes	No-not adjusted for heredity and ETS exposure	Yes	Yes	Yes	Administrative data were not collected for research purposes and lacked individual-level information (e.g. SES measures); exposure misclassification: exposures in microenvironments other than the homes during pregnancy were not considered; no formal comparison of pregnancy and postnatal exposures was conducted in the absence of linked residential histories throughout the follow-up period; not adjusted for heredity and ETS exposure	High
Nishimura[9] (Study 23)	Yes	Yes-cohort better	No-an ethnic minority	no-an ethnic minority	Yes	Yes	Yes	No-an ethnic	Yes	An ethnic minority population: Latino and African American races;	Moderate

			population; self/parents reported outcomes	population; matched cases/controls by geographical area/recruitment centre				minority children		case definition based on self/parent-reported information; less complete regional monitoring of $PM_{2.5}$; reduced accuracy in exposure estimates: Puerto Rico has only 2 monitoring stations; no personal air sampling; no measurement of indoor or prenatal air pollution; case-control matched by geographical region/area	

230 **Abbreviations:** ETS, environmental tobacco smoke; SES, socioeconomic status; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 µm

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Notes for CASP quality assessment of all included studies

The Critical Appraisal Skills Programme (CASP) checklists provided 12 and 11 questions for cohort[2] and case control studies,[3] respectively. It evaluated the internal and external validity of the studies including selection bias, classification, measurement or recall bias for exposure and outcome assessment, adjustment for important confounding factors, the completion and length of follow-up and other characteristics regarding the relevance and generalisation of the results. Important confounding factors were maternal smoking during pregnancy or environmental tobacco smoke (ETS) exposure, heredity and socio-economic status (SES).[26] Any follow-up of children who were less than 6 years of age was considered insufficient as asthma diagnosis for preschool children is challenging.[27]

Due to the fact that there is no scoring system for CASP checklist, we defined articles as having high quality if there were ≥ 7 positive answers to the questions in the CASP checklists, moderate quality if there were ≥ 4 positive answers to the questions, and poor quality if there were ≤ 3 positive answers to the questions.

All studies clearly stated their focused issues on the associations between prenatal and infant $PM_{2.5}$ exposure and the subsequent development of wheezing or asthma. There were no information on recruitment method and comparisons between the cohorts and general population in 5 studies.[12-14, 17, 19] More than half of the studies (n = 10) were considered with potential for selection bias because of low recruitment rates (< 80%),[4, 8, 17-18, 20] only including a small high-risk population [11], inappropriate matching method in a case-control study and different characteristics between participants and non-participants (i.e. ethnicity, maternal age, SES, parental smoking status, heredity, perinatal outcomes).[4, 8-9, 15-16, 18, 20-21] The differences between participants and non-participants may affect the generalisability of

the results in those studies. $PM_{2.5}$ was objectively measured in all studies despite potential exposure misclassifications acknowledged in 7 studies,[5-6, 9, 11, 16, 18, 20] while wheezing or asthma status was defined based on parental or self-reports in most studies (n = 13), which might lead to information bias. There were 5 studies without adjustment for maternal smoking or ETS exposure,[5-7, 10-11] 3 studies without adjustment for heredity[4-6] and 2 studies without adjustment for SES.[18, 21] The overall follow-up was complete among most studies except 4 with ≥ 30% loss to follow-up,[11, 14, 19, 21] whilst the follow-up period was generally short with only 6 studies following the participants for over 6 years.[4, 8, 10-11, 18, 21]

Overall, all the included studies had fairly good qualities for assessing the association between prenatal and infant $PM_{2.5}$ exposure and wheezing or asthma development.

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

Study Reference	**$PM_{2.5}$ increment ($\mu g \cdot m^{-3}$)**	**Original risk estimates (adjusted OR/RR/HR/RD, 95%CI)**
Lee[4] (Study 12)	Prenatal exposure: 1.7	Asthma from birth to age 6: **1.17 (1.04 to 1.30)** **Stratified analyses:** Prenatal maternal stress: high prenatal stress group: **1.15 (1.03 to 1.26)** low prenatal stress group: not significant (no data) gender & prenatal maternal stress: males born to mothers experiencing high stress: **1.28 (1.15 to 1.41)** other groups: not significant (no data)
Sbihi[5] (Study 13)	Prenatal exposure: preschool age asthma: 1.45; school age asthma: 1.46	Asthma from birth to 6 (preschool): 0.99 (0.97 to 1.01) Asthma from 6 t o10 (school age): 1.01 (0.97 to 1.06) **Stratified analyses (preschool asthma):** gender: stronger effects in females than in males (no data) birthweight: stronger effects in children with birthweight < 2500 g than those with birthweight ≥ 2500 g (no data) gestational age: similar effects in both groups (no data)

		maternal age: stronger effects in children with old mothers than those with young mothers (no data) parity: similar effects in both groups (no data) SES: similar effects in both groups (no data)
Clark[6] (Study 20)	Prenatal and infant exposure: 1	Prenatal exposure: asthma from age 3 to 4: IDW: 0.95 (0.91 to 1.00); LUR: 1.02 (1.00 to 1.03) Infant exposure: asthma from age 3 to 4: IDW: 1.05 (0.97 to 1.14); LUR: 1.01 (0.99 to 1.03) **Stratified analyses:** gender: prenatal exposure: males: IDW: 0.94 (0.88 to 1.00); LUR: 1.01 (0.99 to 1.03) females: IDW: 0.98 (0.91 to 1.05); LUR: 1.03 (1.00 to 1.06) infant exposure: males: IDW: 1.02 (0.92 to 1.13); LUR: 1.00 (0.98 to 1.02) females: IDW: 1.10 (0.96 to 1.26); LUR: 1.03 (1.00 to 1.06)
Chiu[7] (Study 21)	Prenatal exposure: high/low exposure (> 11.22 vs ≤ 11.22); low exposure as reference	Repeated wheeze from birth to 2: **2.02 (1.20 to 3.40)** Wheezing category (0-1, 2,or ≥ 3) from birth to 2: multinominal logit models: 2 vs 0-1: **2.01 (1.04 to 3.88)**, ≥ 3 vs 0-1: 2.03 (0.98 to 4.41); adjacent-categories logit models: 2 vs 0-1: **1.55 (1.10 to 2.19)**, ≥ 3 vs 0-1: **2.40 (1.20 to 4.79)** Wheezing category (0-1, 2-3, or ≥ 4) from birth to 2: multinominal logit models: 2-3 vs 0-1: **1.46 (1.02 to 2.10)**, ≥ 4 vs 0-1: **15.5 (2.61 to 92.5)**; adjacent-categories logit models: 2-

		3 vs 0-1: **2.09 (1.33 to 3.27)**, ≥ 4 vs 0-1: **4.36 (1.77 to 10.69)**
Hsu[8] (Study 22)	Prenatal exposure: 10	No data **Stratified analyses:** gender: associations were stronger in males than in females (**interaction p = 0.01**)
Nishimura[9] (Study 23)	Infant exposure: 1	Asthma from age 8 to 21: 1.03 (0.90 to 1.18) **Stratified analyses:** gender: males (280 cases + 212 controls): 0.92 (0.73 to 1.16) females (218 cases + 222 controls): 1.13 (0.98 to 1.30) total IgE: > 200 IU/mL (292 cases + 200 controls): 1.06 (0.93 to 1.21) ≤ 200 IU/mL (221 cases + 235 controls): 1.00 (0.85 t o1.17) family history of asthma: yes (168 cases + 64 controls): 1.05 (0.87 to 1.26) no (262 cases + 340 controls): 0.96 (0.77 to 1.21)
Pennington[10] (Study 24)	Prenatal and infant exposure: natural log-transformed $PM_{2.5}$: 2.7-fold increase; continuous $PM_{2.5}$: 1; quintiles (quintile 1 as reference); Cox proportional hazards regression for infant $PM_{2.5}$ exposure: 2.7-fold increase	Asthma definition: 1 asthma diagnosis + 1 medication dispensing **Cumulative asthma incidence:** Prenatal exposure (natural log-transformed): age 2: **0.015 (0.003 to 0.027)** age 3: **0.018 (0.002 to 0.035)** age 4: **0.023 (0.001 to 0.044)** age 5: **0.032 (0.007 to 0.065)**

		age 6: **0.035 (0.006 to 0.065)** Prenatal exposure (continuous): age 2: 0.005 (-0.002 to 0.011) age 3: 0.004 (-0.005 to 0.013) age 4: 0.007 (-0.005 to 0.018) age 5: 0.009 (-0.005 to 0.023) age 6: 0.010 (-0.007 to 0.027) Prenatal exposure (quintiles): age 5: quintile 2: **0.048 (0.014 to 0.082)** quintile 3: 0.025 (-0.009 to 0.059) quintile 4: **0.057 (0.020 to 0.094)** quintile 5: **0.042 (0.001 to 0.083)** Infant exposure (natural log-transformed): age 2: 0.012 (0.000 to 0.023) age 3: **0.019 (0.003 to 0.034)** age 4**: 0.025 (0.004 to 0.046)** age 5: **0.041 (0.016 to 0.066)** age 6: **0.035 (0.005 to 0.064)** Infant exposure (continuous):

		age 2: 0.003 (-0.004 to 0.010) age 3: 0.004 (-0.005 to 0.013) age 4: 0.008 (-0.005 to 0.020) age 5: 0.013 (-0.002 to 0.028) age 6: 0.009 (-0.009 to 0.027) Infant exposure (quintiles): age 5: quintile 2: **0.049 (0.017 to 0.081)** quintile 3: **0.044 (0.011 to 0.077)** quintile 4: **0.064 (0.029 to 0.100)** quintile 5: **0.054 (0.014 to 0.094)** Infant exposure (Cox proportional hazards regression): age 5: **1.16 (1.07 to 1.26)** Infant exposure (different asthma definitions): age 5: 1 asthma or wheeze diagnosis: **0.037 (0.011 to 0.064)** 1 asthma diagnosis: **0.047 (0.022 to 0.072)** 2 asthma diagnoses: **0.034 (0.012 to 0.056)** 3 asthma diagnoses: **0.031 (0.009 to 0.052)** 2 asthma diagnoses OR 1 acute asthma diagnosis: **0.039 (0.016 to 0.062)**

		1 asthma diagnosis OR 2 medication dispensings: **0.039 (0.012 to 0.067)** 1 asthma diagnosis AND 2 medication dispensings: **0.042 (0.018 to 0.066)** 1 asthma diagnosis OR 1 controller dispensing: **0.048 (0.022 to 0.074)** 1 asthma diagnosis AND (2 reliever dispensings OR 1 controller dispensing): **0.040 (0.016 to 0.064)** Any of the following: a) 1 asthma diagnosis AND 1 medication dispensing in the same year, b) 1 asthma-related emergency department visit or hospitalisation, c) 3 asthma diagnoses: **0.043 (0.018 to 0.068)** **Persistent asthma by age 5 (incident asthma with evidence of asthma in the past year):** Prenatal exposure (natural log-transformed): **0.044 (0.023 to 0.064)** Prenatal exposure (quintiles): quintile 2: **0.039 (0.008 to 0.070)** quintile 3: **0.037 (0.005 to 0.068)** quintile 4: **0.059 (0.025 to 0.094)** quintile 5: **0.055 (0.017 to 0.093)**

		Infant exposure (natural log-transformed): **0.045 (0.023 to 0.066)** Infant exposure (quintiles): quintile 2: **0.041 (0.012 to 0.070)** quintile 3: **0.047 (0.017 to 0.078)** quintile 4: **0.060 (0.027 to 0.093)** quintile 5: **0.054 (0.016 to 0.092)** **Stratified analyses for infant exposure and asthma by age 5 (2.7-fold increase):** gender: males: 0.027 (-0.011 to 0.066) females: **0.047 (0.014 to 0.080)** race: white children: **0.053 (0.017 to 0.089)** black children: **0.048 (0.005 to 0.091)** maternal asthma: yes (n = 1,140): 0.027 (-0.052 to 0.107) no (n = 6,606): **0.041 (0.012 to 0.069)**
Carlsten[11] (Study 25)	Infant exposure: 4.1	Asthma diagnosed at age 7: **3.10 (1.30 to 7.40)**
Jedrychowski[12] (Study 26)	Prenatal exposure: high/low exposure (> 35.30 vs ≤ 35.30), low exposure as reference	Number of days wheezing from birth to 2: **1.36 (1.29 to 1.43)**
Jedrychowski[13]	Prenatal exposure: higher/medium/low exposure (>	Number of days wheezing from birth to 2: higher exposure: **1.62 (1.42 to 1.86)**; medium

(Study 27)	53.40/35.30-53.40 vs ≤ 35.30), low exposure as reference	exposure: **1.13 (1.03 to 1.23)**
Jedrychowski[14] (Study 28)	Prenatal exposure: high/low exposure (> 33.40 vs ≤ 33.40), low exposure as reference	Number of days wheezing from birth to 2: Poisson portion (IRR): **1.38 (1.25 to 1.51);** logistic portion (1/OR): 1.32 (0.84 to 2.08) Number of days wheezing from age 3 to 4: Poisson portion (IRR): 1.06 (0.92 to 1.22); logistic portion (1/OR): 1.03 (0.60 to 1.77)
Gehring[15] (Study 29)	Infant exposure: 1.5	Asthmatic/spastic/obstructive bronchitis from birth to 1: 0.98 (0.80 to 1.20) Asthmatic/spastic/obstructive bronchitis from age 1 to 2: 0.92 (0.78 to 1.09) Wheezing from birth to 1: 0.91 (0.76 to 1.09) Wheezing from age 1 to 2: 0.96 (0.83 to 1.12) **Stratified analyses:** gender: asthmatic/spastic/obstructive bronchitis from birth to 1: males (n = 845): 0.97 (0.76 to 1.25) females (n = 761): 0.98 (0.68 to 1.41) asthmatic/spastic/obstructive bronchitis from age 1 to 2: males (n = 791): 0.92 (0.74 to 1.14) females (n = 719): 0.91 (0.68 to 1.21) wheezing from birth to 1: males (n = 844): 0.91 (0.72 to 1.16) females (n = 753): 0.94 (0.70 to 1.27)

		wheezing from age 1 to 2: males (n = 801): 0.93 (0.76 to 1.14) females (n = 716): 1.04 (0.83 to 1.30)
Morgenstern[16] (Study 30)	Infant exposure: 1.04	Asthmatic/spastic/obstructive bronchitis from birth to 1: 1.04 (0.90 to 1.19) Asthmatic/spastic/obstructive bronchitis from age 1 to 2: 1.05 (0.92 to 1.20) Wheezing from birth to 1: 1.01 (0.87 to 1.18) Wheezing from age 1 to 2: 1.10 (0.96 to 1.25)
Brauer[17] (Study 31)	Infant exposure: 3.2	Asthma from age 1 to 2: 1.12 (0.84 to 1.50) Wheezing from age 1 to 2: 1.14 (0.98 to 1.34)
Yap[18] (Study 32)	Prenatal exposure: 25	Asthma from birth to 10: 4-7th gestational weeks exposure: 0.75 (0.50 to 1.13) 16-20th gestational weeks exposure: 1.38 (0.99 to 1.93) 24-27th gestational weeks exposure: **1.52 (1.08 to 2.15)** 32-35th gestational weeks exposure: **1.89 (1.35 to 2.64)**
Rosa[19] (Study 33)	Prenatal exposure: 3.8	Ever wheeze from birth to 4: not significant for any trimester exposure (no data) Current wheeze at age 4: not significant for any trimester exposure (no data) **Stratified analyses:** Prenatal stress: Ever wheeze from birth to 4: Low stress group:

		1st trimester: 0.99 (0.83 to 1.18) 2nd trimester: 0.92 (0.76 to 1.12) 3rd trimester: 0.96 (0.82 to 1.13) High stress group: 1st trimester: 1.18 (0.97 to 1.43) 2nd trimester: 1.06 (0.85 to 1.32) 3rd trimester: 0.94 (0.78 to 1.15) Current wheeze at age 4: Low stress group: 1st trimester: 0.84 (0.61 to 1.16) 2nd trimester: 0.74 (0.54 to 1.04) 3rd trimester: 0.96 (0.74 to 1.26) High stress group: 1st trimester: **1.35 (1.00 to 1.83)** 2nd trimester: 0.99 (0.71 to 1.38) 3rd trimester: 0.83 (0.61 to 1.13)
Gehring[20] (Study 34)	Infant exposure: 5	Asthma incidence: from birth to 1: 0.87 (0.65 to 1.16) Asthma incidence: from age 1 to 2: **1.38 (1.03 to 1.84)** Asthma prevalence: from birth to 1: 0.97 (0.72 to 1.32)

		Asthma prevalence: from age 1 to 2: **1.38 (1.03 to 1.86)**
MacIntyre[21] (Study 35)	Infant exposure: 1	Ever asthma from birth to 8: 1.03 (0.89 to 1.20) Current asthma at age 6 to 8: **1.35 (1.07 to 1.70)** Ever wheeze from birth to 8: 1.00 (0.87 to 1.14) Current wheeze from birth to 8: 1.18 (0.98 to 1.43) Ever asthma and current wheeze at age 6 to 8: 1.22 (0.98 to 1.52) **Stratified analyses:** genotype: ever asthma from birth to 8: GSTP1 rs1138272: TT/TC: 1.03 (0.67 to 1.60) CC: 1.02 (0.87 to 1.21) GSTP1 rs1695: GG/GA: 0.97 (0.77 to 1.23) AA: 1.09 (0.89 to 1.33) TNF rs1800629: AA/AG: 1.07 (0.77 to 1.48) GG: 1.03 (0.86 to 1.23) current asthma at age 8: GSTP1 rs1138272: TT/TC: **2.19 (1.03 to 4.65)** CC: **1.29 (1.01 to 1.65)** GSTP1 rs1695: GG/GA: 1.19 (0.76 to 1.85) AA: **1.40 (1.06 to 1.84)**

		TNF rs1800629: AA/AG: 1.34 (0.87 to 2.05) GG: **1.42 (1.04 to 1.93)** ever wheeze from birth to 8: GSTP1 rs1138272: TT/TC: 1.14 (0.75 to 1.74) CC: 0.97 (0.83 to 1.12) GSTP1 rs1695: GG/GA: 0.98 (0.80 to 1.21) AA: 1.02 (0.84 to 1.24) TNF rs1800629: AA/AG: 1.04 (0.77 to 1.39) GG: 0.99 (0.84 to 1.16) current wheeze at age 6 to 8: GSTP1 rs1138272: TT/TC: 1.56 (0.90 to 2.72) CC: 1.15 (0.94 to 1.41) GSTP1 rs1695: GG/GA: 1.14 (0.85 to 1.54) AA: 1.20 (0.96 to 1.52) TNF rs1800629: AA/AG: 1.26 (0.86 to 1.85) GG: 1.17 (0.93 to 1.47) ever asthma plus current wheeze at age 6 to 8: GSTP1 rs1138272: TT/TC: **1.95 (1.09 to 3.50)** CC: 1.15 (0.91 to 1.46)

		GSTP1 rs1695: GG/GA: 1.17 (0.80 to 1.72) AA: 1.22 (0.95 to 1.56) TNF rs1800629: AA/AG: 1.32 (0.89 to 1.95) GG: 1.24 (0.94 to 1.63)

Abbreviations: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; OR, odds ratio; RR, risk ratio; HR, hazard ratio; RD, risk difference; 95%CI, 95% confidence interval; IRR, incidence rate ratio. Significant results were shown in bold.

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