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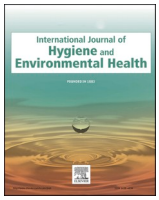

Prenatal exposure to ambient air pollution and subsequent risk of lower respiratory tract infections in childhood and adolescence: A systematic review

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ABSTRACT

Background: Pregnancy represents a critical window of vulnerability to the harmful effects of air pollution on health. However, long-term consequences such as risk of having lower respiratory tract infections (LRTIs) are less explored. This systematic review aims to synthesize previous research on prenatal exposure to ambient (outdoor) air pollution and LRTIs in childhood and adolescence.

Methods: We systematically searched Embase, MEDLINE, Web of Science Core Collection, CINAHL, and Global Health up to May 17, 2024. We included peer-reviewed publications of studies which investigated the association between prenatal exposure to ambient air pollution and LRTIs up to the age of 19. We excluded conference abstracts, study protocols, review articles, and grey literature. Screening and data extraction was conducted by two reviewers independently. We used the Office of Health Assessment and Translation tool to assess risk of bias and conducted a narrative synthesis.

Results: The search yielded 6056 records, of which 16 publications describing 12 research studies were eligible for the synthesis. All studies were conducted in high- or upper-middle-income countries in Europe or Asia. Half (6) of the studies focused on LRTIs occurring within the first three years of life, and the others also included LRTIs in older children (up to age 14). Air pollutants investigated included nitrogen dioxide, sulphur dioxide, particulate matter ($PM_{2.5}$: diameter $\leq$2.5 μm and PM_{10}: diameter $\leq$10 μm), carbon monoxide, ozone, and benzene. Findings on a potential association between prenatal ambient air pollution exposure and LRTIs were inconclusive, without a clear and consistent direction. There was some suggestion of a positive association with prenatal $PM_{2.5}$ exposure. The small number of studies identified, their poor geographical representation, and their methodological limitations including concerns for risk of bias preclude more definitive conclusions.

Conclusion: The available published evidence is insufficient to establish whether prenatal exposure to ambient air pollution increases risk of LRTIs in children and adolescents. With many populations exposed to high levels of air

Abbreviations: C_6H_6, benzene; CI, confidence interval; CO, carbon monoxide; COSTER, Conduct of Systematic Reviews in Toxicology and Environmental Health Research; ICD, International Classification of Disease; LRTI, lower respiratory tract infection; NO_2, nitrogen dioxide; OHAT, Office of Health Assessment and Translation; OR, odds ratio; O_3, ozone; $PM_{2.5}$, particulate matter with a diameter $\leq$2.5 μm; $PM_{2.5\text{-}10}$, particulate matter with a diameter $\leq$10 μm but >2.5 μm; PM_{10}, particulate matter with a diameter $\leq$10 μm; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; PSI, Pollution Standard Index; SO_2, sulphur dioxide; WHO, World Health Organization.

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pollution, there is an urgent need for research in more diverse settings, more transparent reporting of methods, and exploring how, when, and for whom prenatal exposure to ambient air pollution leads to the greatest health risks.
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1. Introduction

Breathing clean air has been declared a human right by the United Nations General Assembly (United Nations Environment Programme, 2022), recognising the pervasive threat of poor air quality to human health. Nevertheless, the majority of the world's population continues to be exposed to air pollution levels exceeding the World Health Organization's (WHO) 2021 Air Quality Guidelines (World Health Organization, 2021). For example, only 10% of countries met the WHO target for fine particulate matter (diameter $\leq$2.5 μm; recommended annual level $\leq$5 μg/m^3) as of 2022 (Wise, 2023). Ambient air pollution is contamination of the 'outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere' (World Health Organization, n.d., ll. 1–2), and pregnancy represents a period of vulnerability to its harmful effects (World Health Organization, 2021).

Recent reviews provided evidence of links between ambient air pollution and adverse maternal (Mazumder et al., 2024) and adverse pregnancy outcomes (Nyadanu et al., 2022). However, the long-term impacts of prenatal exposure to ambient air pollution on children and adolescents are much less explored, especially a potential association with lower respiratory tract infections (LRTIs).

The long-term consequences of prenatal exposure to air pollution are likely to include compromised respiratory health, as exposure to air pollution during pregnancy has been hypothesized to affect lung development (Hsu et al., 2023; Neophytou et al., 2023; Pinkerton and Joad, 2006) and modify expression of genes that influence epithelial inflammation (Esposito et al., 2014). Moreover, systematic reviews have previously found childhood asthma and wheezing to be associated with prenatal exposure to some air pollutants, such as nitrogen oxides and particulate matter (Bettiol et al., 2021; Hehua et al., 2017). Prenatal air pollution exposure has also been suggested to increase susceptibility to airway infection in children (Yadav and Pacheco, 2023), but no review has yet explored this relationship systematically. Given that pneumonia is one of the leading causes of global under-five mortality (World Health Organization, 2022a), there is an urgent need to understand the contribution of air pollution to LRTIs. This systematic review aims to synthesize previous research on the association between prenatal exposure to ambient air pollution and risk of LRTIs in childhood and adolescence.

2. Methods

The protocol for this systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews; ID: CRD42023407689). The COSTER (Conduct of Systematic Reviews in Toxicology and Environmental Health Research) recommendations (Whaley et al., 2020) informed the planning and conduct of the systematic review and the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Page et al., 2021) guided the reporting.

To identify studies addressing the research questions, we applied the PECOS framework (Population, Exposure, Comparator, and Outcomes, Study Design; Table 1) (Morgan et al., 2018; Nyadanu et al., 2020).

2.1. Search

We searched for studies investigating the association between prenatal exposure to ambient air pollution and LRTIs in five databases (EBSCOhost CINAHL Complete, Ovid Embase, Ovid Global Health, Ovid MedlineALL, Clarivate Analytics Web of Science Core Content) on May 5, 2023, without restricting on year of publication. To update our search findings, we re-ran the search on May 17, 2024, and restricted this search to records published since January 1, 2023. The search strategy combined search terms related to the exposure (ambient air pollution), the exposure period (during pregnancy), and the outcome (LRTIs in childhood and adolescence) with the Boolean operator AND (for the full search strategy, see Appendix). To identify articles on ambient air pollution, we included general search terms (e.g., air quality) in addition to searching for individual air pollutants drawing from WHO guidelines and reports (WHO Regional Office for Europe, 2023; 2021; World Health Organization, 2021). For LRTIs, our search terms covered clinical manifestations (e.g., pneumonia) as well as common pathogens affecting the age group of interest (e.g., respiratory syncytial virus (Reeves et al., 2017)). The search was run without restricting language or geography. In addition, we screened the reference lists of included articles.

2.2. Eligibility

Publications were eligible if they reported on population, exposure, comparator, outcome and study design that matched our PECOS statement (Table 1). Where studies reported on individual diseases (e.g., bronchitis), we consulted the International Classification of Disease (ICD; 10th Revision) to assess their classification as a LRTI. Given the lag between exposure (prenatal) and outcome (postnatal), we expected that individual-level data would be required to properly adjust for potential confounders (e.g., socioeconomic status) and to reduce the risk of ecological fallacy. Furthermore, to be included, publications needed to 1) be peer-reviewed, and 2) present an effect estimate for the association of prenatal exposure to ambient air pollution with LRTIs. We excluded study protocols, conference abstracts, review articles and grey literature. We also excluded studies on wildfires because the composition of

Table 1
PECOS statement.

PECOS element	Eligibility criteria
Population	Children and adolescents (i.e., individuals up to 19 years of age as defined by the WHO (World Health Organization, n.d.))
Exposure	Prenatal exposure to ambient air pollution exposure *"Prenatal exposure" was defined as exposure assessed at any point/period during pregnancy, EXCLUDING exposure periods which are not pregnancy-specific.* *"Ambient air pollution exposure" was defined as a measure of the concentration of one, multiple or a mixture of outdoor air pollutants (as defined by study authors; including proxies, such as distance to roads), EXCLUDING household (indoor) and wildfire exposure.*
Comparator	Children and adolescents exposed to lower levels of ambient air pollution during pregnancy compared to more highly exposed children and adolescents.
Outcome	Incidence of LRTIs including specific complications (e.g., pneumonia) as well as broader categories (e.g., chest infections) independent of mode of ascertainment, EXCLUDING outcome definitions which combine upper and lower respiratory tract infections.
Study Design	Individual-level observational studies, such as cohort or case-control studies.

wildfire smoke is likely to differ from other sources of air pollution (Black et al., 2017).

2.3. Screening and extraction

We imported records identified by the database searches to the systematic review software Rayyan (Ouzzani et al., 2016). Using the Rayyan deduplication feature, we identified likely duplicates before checking and removing them.

Two reviewers (MP, IF) independently screened titles and abstracts, and then assessed the full text of potentially relevant papers for eligibility. A third reviewer (ESP) advised on conflicting decisions. Using a standardised Excel form, two reviewers (MP, PR) independently extracted information on the study details (design as described by authors, location, population, sample size, date of data collection), the exposure definition (type of pollutants, ascertainment method, exposure window), the outcome definition (condition, time and method of ascertainment), measures of association (with error estimates), and covariates from eligible papers. During data extraction, we observed that some publications reported findings from multiple statistical models. We decided to extract measures of association from the model with the greatest number of variables (i.e., the fully adjusted model).

2.4. Risk of bias assessment

For each of the included publications, we evaluated the risk of bias using a tool developed by the Office of Health Assessment and Translation (OHAT) (National Toxicology Program, 2019) which was designed specifically for environmental health research (Michel et al., 2024). Cohort and case-control studies were rated based on three key and four additional criteria with response options including 1) definitely low risk of bias 2) probably low risk of bias 3) probably high risk of bias and 4) definitely high risk of bias. The key criteria were detection bias in exposure characterisation, detection bias in outcome assessment, and confounding bias. Additional criteria were selection bias, attrition/exclusion bias, selective reporting bias, and other sources of bias. Two reviewers (MP, PR) first rated the studies independently and then a consensus decision was reached through discussion (MP, PR, ESP). Applying the guidance provided by OHAT, publications were classified as Tier 1 when they were rated 'definitely low' or 'probably low' across the three key criteria and were rated 'definitely low' or 'probably low' across most of the other criteria. Publications were classified as Tier 3 when they were rated 'definitely high' or 'probably high' across the three key criteria and rated 'definitely high' or 'probably high' across most of the other criteria. All other publications were classified as Tier 2. Additional details on the criteria used to assess risk of bias was presented in Table A.1.

2.5. Evidence synthesis

Due to the small number of studies identified for a given pollutant and the differences in outcome definitions and length of follow-up across the included studies, we conducted a narrative synthesis. Based on the description of the study name, setting, population, and exposure variables, we identified publications related to the same research study. Aligning with the COSTER recommendations (Whaley et al., 2020), we extracted information from all the eligible publications, but grouped publications describing the same research study in the synthesis (i.e., the unit of evidence is the research study, rather than the publications describing it). Within the Results section, we report the direction of the detected effects (positive: point estimate >1.00, negative: point estimate <1.00) and general patterns of associations (focused on exposure during the full pregnancy and specific trimesters) across all studies. Within the main results table, we focus on associations which were statistically significant at the 5% significance level. All the extracted information is available in the Appendix.

2.6. Protocol amendments

Post-hoc modifications of the initial review protocols included 1) expanding the age range of study participants to 19 years of age (vs. 17 years of age) to align with the WHO definition of adolescents (World Health Organization, n.d.), 2) adopting the OHAT tool for risk of bias assessment (vs. the Newcastle-Ottawa Scale) as it is better suited for environmental health research (Michel et al., 2024), and 3) not conducting a meta-analysis or subgroup analyses due to the observed heterogeneity and small number of studies identified.

3. Results

The search strategy identified a total of 6056 records of which 16 publications from 12 research studies were included in the synthesis (Fig. 1; see Figure A.1 for a description of the search and selection process for the initial and updated search separately). There were 35 publications which underwent full text review but were excluded from the synthesis (see Table A.2). For three research studies, we included more than one publication: the Spanish INMA cohort (INMA-INfancia y Medio Ambiente) (Aguilera et al., 2013; Esplugues et al., 2011; Gutiérrez Oyarce et al., 2018), the CCHH (China, Children, Homes, Health) study in Shanghai (Liu et al., 2016, 2020), and a case-control study at XiangYa Hospital in Changsha (Lu et al., 2021; Yang et al., 2023).

3.1. Study settings, study designs, and study participants

The characteristics of the included 12 research studies (16 individual publications) are presented in Table 3. All studies were conducted in countries in Asia or Europe; five studies in China (Jiang et al., 2018; Liu et al., 2016, 2020, 2022; Lu et al., 2021, 2023; Yang et al., 2023) and the others in Singapore (Soh et al., 2018), Spain (Aguilera et al., 2013; Esplugues et al., 2011; Gutiérrez Oyarce et al., 2018), Poland (Jedrychowski et al., 2013), Norway (Madsen et al., 2017), France (Zhou et al., 2013), Finland (Belachew et al., 2024), and Israel (Goshen et al., 2020). No study was conducted in a lower-middle or low-income country. Except for one case-control study (Lu et al., 2021; Yang et al., 2023), all studies were cohort studies. Study participants were recruited between 1991 (Belachew et al., 2024) and 2020 (Lu et al., 2023). Sample sizes ranged from 214 (Jedrychowski et al., 2013) to 17,533 individuals (Madsen et al., 2017).

3.2. Ambient air pollution measurement

The studies investigated a range of different air pollutants, namely nitrogen dioxide (NO_2), sulphur dioxide (SO_2), particulate matter ($PM_{2.5}$: diameter ≤2.5 μm, $PM_{2.5\text{-}10}$: diameter ≤10 μm but >2.5 μm, PM_{10}: diameter ≤10 μm), ozone (O_3), carbon monoxide (CO), and benzene (C_6H_6). NO_2 was most frequently investigated (8 studies) (Aguilera et al., 2013; Belachew et al., 2024; Esplugues et al., 2011; Gutiérrez Oyarce et al., 2018; Jiang et al., 2018; Liu et al., 2016, 2020, 2022; Lu et al., 2021, 2023; Madsen et al., 2017; Yang et al., 2023). One study investigated traffic density near the home as a proxy of traffic-related air pollution exposure (Zhou et al., 2013). Another study assessed the Pollution Standard Index (PSI), an indicator of air quality reflecting five pollutants (PM_{10}, SO_2, NO_2, CO, and O_3) (Soh et al., 2018).

Ascertainment of air pollution exposures varied across studies (see Table A.3) and included data from: personal environmental monitoring samplers (Jedrychowski et al., 2013), air sampling campaigns in the study areas (Aguilera et al., 2013; Esplugues et al., 2011; Gutiérrez Oyarce et al., 2018; Madsen et al., 2017), local air quality monitoring stations (Goshen et al., 2020; Jiang et al., 2018; Liu et al., 2016, 2020, 2022; Lu et al., 2021, 2023; Soh et al., 2018; Yang et al., 2023), satellite remote sensing (Goshen et al., 2020), modelled data of atmospheric

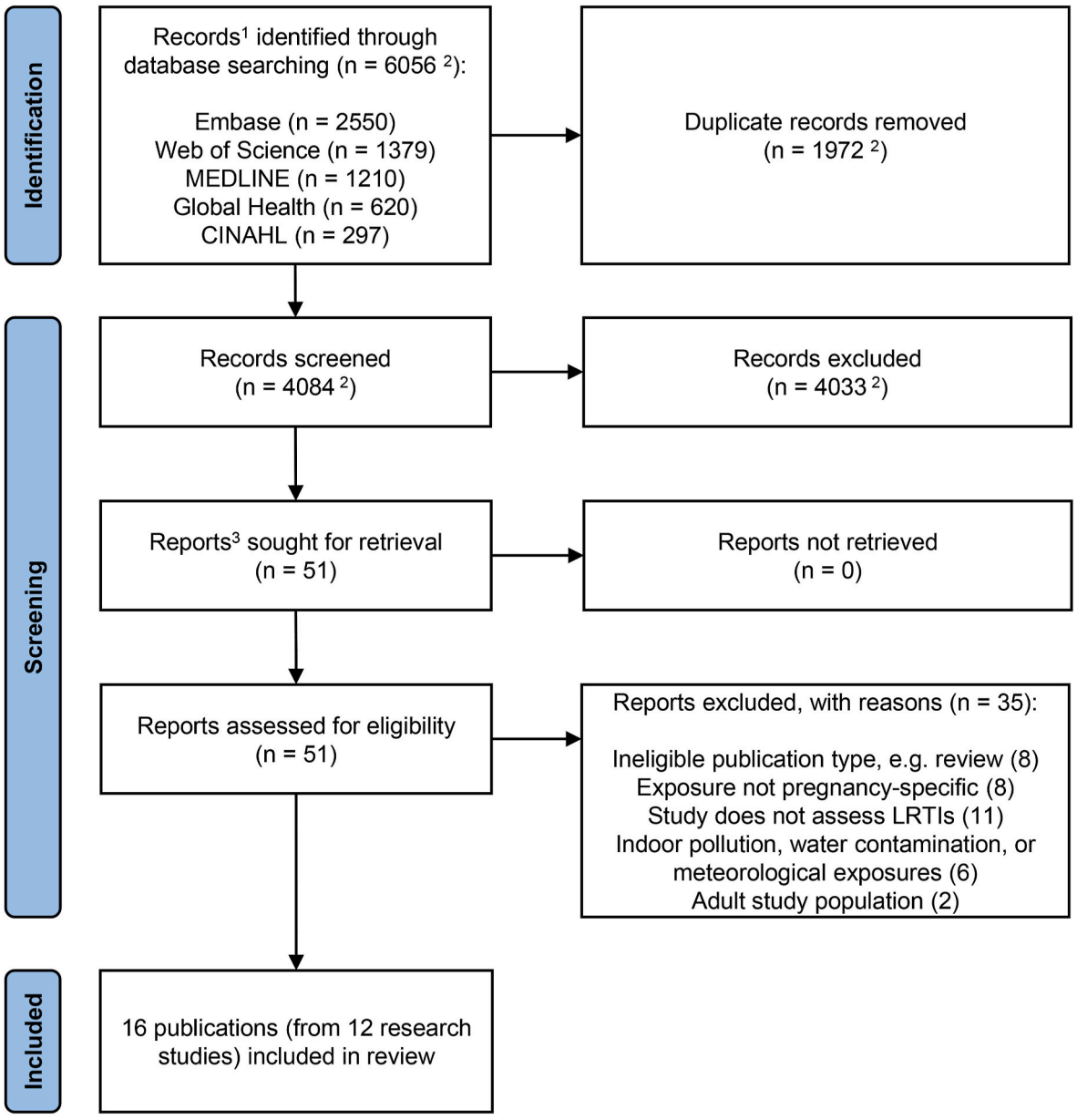

Fig. 1. PRISMA flow diagram.
[1] Record defined as title and abstract of a report indexed in a database.
[2] Here, the reported numbers may be inflated as some records/reports could have been indentified both in the initial and the updated search.
[3] Report defined as a document supplying information aboubt a particular study (full text).

composition (Belachew et al., 2024), and a questionnaire assessing traffic density (Zhou et al., 2013). To estimate exposure at the residential address, studies applied land use regression models (Aguilera et al., 2013; Esplugues et al., 2011; Goshen et al., 2020; Gutiérrez Oyarce et al., 2018; Madsen et al., 2017) and inverse distance weight methods (Jiang et al., 2018; Liu et al., 2022; Lu et al., 2021, 2023; Yang et al., 2023). If information on pregnancy home address was unavailable, studies used air pollution levels (at the time of pregnancy) at the child's current home (Lu et al., 2021, 2023; Yang et al., 2023) or kindergarten address (Jiang et al., 2018; Liu et al., 2022) as a proxy. Two studies estimated exposure at the district/national level, averaging data from local monitoring stations (Liu et al., 2016, 2020; Soh et al., 2018). Where data was available at a daily resolution, daily air pollution estimates were commonly averaged, either across the entire pregnancy (Aguilera et al., 2013; Belachew et al., 2024; Esplugues et al., 2011; Gutiérrez Oyarce et al., 2018; Jiang et al., 2018; Liu et al., 2016, 2020, 2022; Lu et al., 2021, 2023; Madsen et al., 2017; Soh et al., 2018; Yang et al., 2023) or individual trimesters (Aguilera et al., 2013; Esplugues et al., 2011; Goshen et al., 2020; Gutiérrez Oyarce et al., 2018; Liu et al., 2020; Lu et al., 2021, 2023; Soh et al., 2018; Yang et al., 2023).

3.3. *Measurement of lower respiratory tract infections*

LRTI case definitions differed across studies and five of the studies evaluated LRTIs as a grouped outcome. Seven studies focused one (or more) distinct LRTI, with six studies assessing pneumonia (Jiang et al., 2018; Liu et al., 2016, 2020, 2022; Lu et al., 2021, 2023; Soh et al., 2018; Yang et al., 2023) and two assessing bronchiolitis (Soh et al., 2018; Zhou et al., 2013). Only three studies assessed LRTIs based on medical records (Belachew et al., 2024; Goshen et al., 2020; Lu et al., 2021; Yang et al., 2023), with the others relying on caregiver reports. Half (6) of the studies focused on LRTIs occurring within the first three years of life

Table 2
Office of Health Assessment and Translation (OHAT) risk of bias assessment.

			Key criteria						
Study №	Study	Tier	Confounding Bias[1]	Detection Bias Exposure[2]	Detection Bias Outcome[3]	Selection Bias[4]	Attrition/Exclusion Bias[5]	Selective Reporting Bias[6]	Other Sources of Bias[7]
#1	Aguilera 2013	2	+	+	-	+	+	++	++
	Esplugues 2011	2	+	+	-	+	+	++	+
	Gutiérrez Oyarce 2018	2	+	+	-	+	-	-	+
#2	Belachew 2024	1	++	++	++	+	+	-	++
#3	Goshen 2020	2	--	+	++	+	-	++	++
#4	Jedrychowski 2013	2	+	+	-	+	+	-	++
#5	Jiang 2018	2	++	-	-	-	--	-	-
#6	Liu 2020	2	+	-	-	+	NR	++	-
	Liu 2016	2	+	-	-	+	NR	++	-
#7	Liu 2022	2	++	-	-	+	NR	++	-
#8	Lu 2023	2	+	-	-	+	-	++	-
#9	Madsen 2017	2	-	+	-	+	+	+	++
#10	Soh 2018	2	+	-	--	+	-	-	-
#11	Yang 2023	3	--	-	-	--	NR	-	-
	Lu 2021	3	--	-	-	--	NR	-	-
#12	Zhou 2013	2	NR	--	--	+	-	+	+

Definitely low risk of bias (++), Probably low risk of bias (+), Probably high risk of bias (-; NR: not reported), Definitely high risk of bias (–)
[1] Did the study design or analysis account for important confounding and modifying variables?
[2] Can we be confident in the exposure characterization?
[3] Can we be confident in the outcome assessment?
[4] Did selection of study participants result in appropriate comparison groups?
[5] Were outcome data complete without attrition or exclusion from analysis?
[6] Were all measured outcomes reported?
[7] Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?

(Aguilera et al., 2013; Belachew et al., 2024; Esplugues et al., 2011; Goshen et al., 2020; Gutiérrez Oyarce et al., 2018; Madsen et al., 2017; Soh et al., 2018; Zhou et al., 2013), and the others also included LRTIs in older children (up to age 14) (Jedrychowski et al., 2013; Jiang et al., 2018; Liu et al., 2016, 2020, 2022; Lu et al., 2021, 2023; Yang et al., 2023). For further details on the outcome definitions and ascertainment methods, see Table A.3.

3.4. Risk of bias assessment

Across the 16 publications, only one was classified as Tier 1. Two publications were classified as Tier 3, and the others as Tier 2 (Table 2). There was 'probably high' or 'definitely high' risk of detection bias across multiple of the studies, both with regards to the assessment of the exposure and the outcome (Figure A.2). Key concerns related to LRTIs being assessed based on caregiver reports or the lack of accurate information on pregnancy home addresses. Not all studies accounted for a minimum set of relevant confounders, such as socioeconomic status, environmental tobacco smoke exposure, and indoor home environment. Only four studies controlled for postnatal exposure to ambient air pollution (Jiang et al., 2018; Liu et al., 2022; Lu et al., 2023; Soh et al., 2018). The reported follow-up rates ranged from 43 (Jedrychowski et al., 2013) to 88% (Zhou et al., 2013).

3.5. Association of prenatal exposure to ambient air pollution and childhood LRTIs

All studies presented an adjusted effect estimate for the association of prenatal ambient air pollution exposure and LRTIs. Results varied across studies, with some reporting positive associations and others reporting negative associations, often with wide confidence intervals (Table 3). Six studies investigated trimester-specific associations between ambient air pollution and LRTIs (Aguilera et al., 2013; Esplugues et al., 2011; Goshen et al., 2020; Gutiérrez Oyarce et al., 2018; Liu et al., 2020; Lu et al., 2021, 2023; Soh et al., 2018; Yang et al., 2023), but the evidence on windows of heightened susceptibility was inconclusive. Some studies investigated the effect of air pollution on different population groups (e.g., one finding ethnic disparities in the Negev region where a statistically significant positive association was only observed among the Arab-Bedouin population, as defined by the study authors (Goshen et al., 2020)). Additional details, including crude effect estimates and information on covariates for each study, are provided in Table A.4.

Eight studies investigated a potential association between prenatal exposure to NO_2 and LRTIs. The direction of the reported associations was neither clear nor consistent. For exposure across the entire pregnancy, some studies suggested a positive association (Aguilera et al., 2013; Esplugues et al., 2011; Liu et al., 2016, 2020; Lu et al., 2023) while others suggested a negative association (Jiang et al., 2018; Liu et al., 2022; Lu et al., 2021; Yang et al., 2023). Some studies suggested the direction of the effect to change across trimesters. Only three studies reported statistically significant associations. One showed that a 10 $\mu g/m^3$ increase in exposure to NO_2 during the second trimester was associated with higher risk (RR: 1.08, 95% CI: 1.02 to 1.15) of caregiver-reported LRTI in the first 18 months (Aguilera et al., 2013). Liu et al. (2020) also reported a positive association with pneumonia among children in preschools, however, the third study found a negative association for pneumonia diagnosed by hospital doctors (up to age 14) after adjusting for co-exposure to other pollutants (Lu et al., 2021; Yang et al., 2023).

There were six studies focusing on prenatal exposure to PM_{10}, one study on $PM_{2.5\text{-}10}$, and five studies on $PM_{2.5}$. For $PM_{2.5\text{-}10}$ and PM_{10}, the direction of the reported effects differed across studies, as well as across trimesters within the same study (Liu et al., 2020; Lu et al., 2021; Yang et al., 2023). For $PM_{2.5}$, all five studies reported some positive associations, either for exposure across the entire pregnancy or specific

Table 3
Characteristics of included studies.

Study N°	Reference	Study name[a]	Study design, Country	Sample size	Pollutants and exposure windows	Outcome and age of ascertainment	Effect and effect direction (after adjustment)[b]	Covariates[c]							
								A	B	C	D	E	F	G	H
#1	Aguilera et al., 2013	INMA (4 regions)	Birth cohort, Spain	2199	NO_2, C_6H_6 Estimated for trimesters and entire pregnancy	Caregiver-reported LRTI (up to 18 months)	↑NO_2 ↑C_6H_6 (both only for 2nd trimester exposure)	x	x	x					x
	Esplugues et al., 2011	INMA Valencia	Birth cohort, Spain	352	NO_2 Estimated for trimesters and entire pregnancy	Caregiver-reported LRTI (up to 1 year)	↔NO_2	x		x		x			x
	Gutiérrez Oyarce et al., 2018	INMA Valencia	Birth cohort, Spain	624	NO_2 Estimated for trimesters and entire pregnancy	Caregiver-reported LRTI (up to 2 years)	↔NO_2	x							
#2	Belachew et al., 2024	ECS	Cohort, Finland	2568	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3 Estimated for entire pregnancy	LRTI hospitalisation (from discharge registers; up to 2 years)	↔$PM_{2.5}$ ↔PM_{10} ↔SO_2 ↔NO_2 ↔CO ↔O_3	x	x	x			x	x	
#3	Goshen et al., 2020	*Not reported*	Retrospective cohort, Israel	57,331	$PM_{2.5}$ Estimated for trimesters	First LRTI hospitalisation (from medical charts; up to 1 year)	↑$PM_{2.5}$ (only for 1st and 2nd trimester exposure in Arab-Bedouin population)	x				x	x		
#4	Jedrychowski et al., 2013	*Not reported*	Birth cohort, Poland	214	$PM_{2.5}$ Single point measure: assessed in 2nd trimester	Caregiver-reported recurrent broncho-pulmonary infections (≥5 episodes of bronchitis/ pneumonia; up to 7 years)	↑$PM_{2.5}$	x		x					x
#5	Jiang et al., 2018	CCCH Changsha	Retrospective cohort, China	2598	PM_{10}, SO_2, NO_2 Estimated for entire pregnancy	Caregiver-reported pneumonia (3–6 years)	↔PM_{10} ↔SO_2 ↔NO_2	x	x	x	x	x		x	x
#6	Liu et al., 2020	CCCH Shanghai	Retrospective cohort, China	3177	PM_{10}, SO_2, NO_2 Estimated for trimesters and entire pregnancy	Caregiver-reported pneumonia (4–6 years)	↔PM_{10} ↔SO_2 ↑NO_2 (only for 1st, 2nd, and 3rd trimester exposure)	x	x	x	x	x	x		x
	Liu et al., 2016	CCCH Shanghai	Retrospective cohort, China	3358	PM_{10}, SO_2, NO_2 Estimated for entire pregnancy	Caregiver-reported pneumonia (4–6 years)	↔PM_{10} ↔SO_2 ↔NO_2	x	x	x	x		x		x
#7	Liu et al., 2022	CCCH Shenzhen	Retrospective cohort, China	3226	PM_{10}, SO_2, NO_2 Estimated for entire pregnancy	Caregiver-reported pneumonia (3–6 years)	↔PM_{10} ↔SO_2 ↔NO_2	x	x	x	x	x		x	x
#8	Lu et al., 2023	2nd CCCH Changsha	Retrospective cohort, China	8689	$PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, SO_2, NO_2, CO Estimated for trimesters and entire pregnancy	Caregiver-reported pneumonia (3–6 years)	↑$PM_{2.5}$ (only for 2nd trimester exposure) ↔$PM_{2.5\text{-}10}$ ↔PM_{10} ↔SO_2 ↔NO_2 ↔CO	x	x	x	x	x	x	x	x

(*continued on next page*)

Table 3 (*continued*)

Study N°	Reference	Study name[a]	Study design, Country	Sample size	Pollutants and exposure windows	Outcome and age of ascertainment	Effect and effect direction (after adjustment)[b]	Covariates[c]							
								A	B	C	D	E	F	G	H
#9	Madsen et al., 2017	MoBa	Pregnancy cohort, Norway	17,533	NO_2 Estimated for entire pregnancy	LRTI hospitalisation (reported by caregivers; up to 18 months)	↔NO_2	x	x	x					x
#10	Soh et al., 2018	GUSTO	Birth cohort, Singapore	953	$PM_{2.5}$, PSI Estimated for trimesters and entire pregnancy	Caregiver-reported bronchiolitis/ bronchitis and pneumonia (up to 2 years)	↔$PM_{2.5}$ ↑PSI (only for 1st and 2nd trimester exposure and bronchiolitis/ bronchitis)	x	x	x				x	
#11	Yang et al., 2023	*Not reported*	Case-control study, China	1510	PM_{10}, SO_2, NO_2 Estimated for trimesters and entire pregnancy	Pneumonia diagnosis (from hospital records; up to 14 years)	↔PM_{10} ↑SO_2 ↓NO_2	x	x			x	x	x	
	Lu et al., 2021	*Not reported*	Case-control study, China	1510	PM_{10}, SO_2, NO_2 Estimated for trimesters and entire pregnancy	Pneumonia diagnosis (from hospital records; up to 14 years)	↔PM_{10} ↑SO_2 ↓NO_2	x	x			x	x	x	
#12	Zhou et al., 2013	EDEN	Mother-child cohort, France	1765	Self-reported traffic-related air pollution Single point measure: assessed around birth	Caregiver-reported bronchiolitis (up to 12 months)	↑traffic-related air pollution	*Not reported*							

[a] Full study names: INMA – INfancia y Medio Ambiente, ECS – Espoo Cohort Study, CCCH – China-Children-Homes-Health, MoBa – Norwegian Mother and Child Cohort Study, GUSTO – Growing Up in Singapore towards healthy Outcomes, EDEN mother-child cohort study.

[b] Effect direction: ↑ statistically significant increase in the odds/risk of adverse outcome, ↓ statistically significant decrease in the odds/risk of adverse outcome, ↔ inconsistent results or no statistically significant association. Details on effect estimates and confidence intervals are presented in Table A.4.

[c] Adjusted analysis included covariates related to A: characteristics of the child (e.g., age, sex, birth outcomes), B: characteristics of the parents (e.g., medical history, socioeconomic status), C: environmental tobacco smoking, D: indoor home environment, E: outdoor temperature/season, F: exposure to other pollutants, G: exposure to the same pollutant during other time periods (e.g., postnatally), H: others.

trimesters. However, the confidence intervals were often wide and only three studies reported statistically significant associations (Goshen et al., 2020; Jedrychowski et al., 2013; Lu et al., 2023). For example, Lu et al. (2023) observed that an increment of one interquartile range (28 μg/m^3) in $PM_{2.5}$ exposure increased the odds of caregiver-reported pneumonia children in preschools, but the effect estimates were only statistically significant in the second trimester (OR: 1.18, 95% CI: 1.04 to 1.34).

Six studies investigated prenatal exposure to SO_2. For exposure across the entire pregnancy, there was an equal split between studies suggesting a positive (Belachew et al., 2024; Liu et al., 2016, 2020; Yang et al., 2023) and a negative association (Jiang et al., 2018; Liu et al., 2022; Lu et al., 2023). In two studies, the direction of the effect changed across different trimesters (Liu et al., 2020; Lu et al., 2023). Only one study found a statistically significant association, estimating the odds of physician-diagnosed pneumonia (based on medical records; up to age 14) to increase 4.95-times (95% CI: 3.15 to 7.78) per 10 μg/m^3 increase in SO_2 exposure across the entire pregnancy (Yang et al., 2023).

Furthermore, studies investigated an association between LRTIs and prenatal exposure to C_6H_6 (1 study), CO (2 studies), O_3 (1 study), the Pollution Standard Index (1 study), and traffic-related air pollution (self-reported using a questionnaire; 1 study). For prenatal C_6H_6 exposure, Aguilera et al. (2013) found a 1 μg/m^3 increase in C_6H_6 during the second trimester to be associated with higher risk (RR: 1.10, 95% CI: 1.01 to 1.20) of caregiver-reported LRTIs (up to 18 months of age). For CO and O_3, the reported effect estimates were generally suggestive of a negative association (not statistically significant). For traffic-related air pollution, Zhou et al. (2013) found 51% higher odds (95% CI: 1.18 to 1.92) of caregiver-reported ever bronchiolitis (up to age 1) among children of parents reporting *in utero* exposure to traffic-related air pollution. The study applying the Pollution Standard Index found a positive association between exposure to higher quartiles of the index during the first and second trimester and caregiver-reported bronchiolitis/bronchitis (up to age 2; incidence rate ratio: 1.67, 95% CI: 1.07 to 2.60) (Soh et al., 2018). For pneumonia, the same study found inconsistent results, with the direction of the effect changing across trimesters.

4. Discussion

This systematic review synthesises current evidence on the association between prenatal exposure to ambient air pollution and LRTIs during childhood and adolescence. The identified 12 studies (16 publications) varied with regards to the pollutants investigated, the outcome definitions, and the length of follow-up after birth. Most studies were prone to bias, especially detection bias related to the exposure and the outcome. The identified studies were concentrated in Asia and Europe and no study meeting our criteria was conducted in a lower-middle or low-income country, despite these populations being among those most frequently exposed to unsafe levels of ambient air pollution (i.e., annual average $PM_{2.5}$ concentration $>$ 5 μg/m^3) (Rentschler and Leonova, 2023). Findings on a potential association between prenatal air pollution exposure and LRTIs were inconclusive, without a clear and consistent direction. However, there was some suggestion that prenatal

$PM_{2.5}$ exposure may be associated with an increased risk of LRTIs (Goshen et al., 2020; Jedrychowski et al., 2013; Lu et al., 2023).

Nevertheless, our review offers insights that complement our current understanding of prenatal exposure to air pollution and respiratory infections later in life. The Developmental Origins of Health and Disease theory hypothesises that *in utero* exposure to environmental stressors increases susceptibility to adverse health outcomes throughout the life course (Heindel et al., 2017), for example by *in utero* exposure to air pollution altering DNA methylation with potential impacts on immune or metabolic functions (Gruzieva et al., 2017; Ladd-Acosta et al., 2019). It has been suggested that prenatal exposure to air pollution might influence the developing foetus via two pathways: the pollutants could directly impact the foetus if they were able to enter the blood stream and cross the placental barrier, or they could impact the foetus indirectly (e.g., by causing systemic and placental oxidative stress and inflammation) (Yadav and Pacheco, 2023). Our review found that evidence of an association was most consistent for $PM_{2.5}$ compared to other pollutants. Previous work has shown that fine particles can enter the circulation and cross the placental barrier (Bongaerts et al., 2022; Kaur et al., 2022), thereby offering a potential explanation for how $PM_{2.5}$ could influence foetal development. In terms of indirect pathways, prenatal exposure to air pollution is known to be associated with adverse birth outcomes such as preterm delivery and small for gestational age (Lin et al., 2023; Nyadanu et al., 2022) which in turn have been linked to increased susceptibility to respiratory infections later in life (Coathup et al., 2021; Davidesko et al., 2020; Garioud et al., 2020; Serrano-Lomelin et al., 2021). Despite some included studies collecting data on gestational age, none of them explored this pathway—an omission that future research could address.

Air pollution is a well-established risk factor for respiratory infections, with the WHO estimating that 18% of the 4.2 million premature deaths attributed to ambient air pollution in 2019 were due to acute LRTIs (World Health Organization, 2022b). Among infants and children, systematic reviews have linked exposure to ambient air pollution to both upper (Ziou et al., 2022) and lower respiratory tract infections (Mehta et al., 2013), including severe outcomes such as hospitalisation due to bronchiolitis (King et al., 2018) or pneumonia (Nhung et al., 2017). However, to the best of our knowledge, this is the first systematic review looking specifically at prenatal exposure to air pollution and its potential association with LRTIs. The review thereby adds to other literature on the health effects of prenatal air pollution exposure, such as adverse maternal and birth outcomes (Mazumder et al., 2024; Nyadanu et al., 2022), non-communicable respiratory health outcomes (Bettiol et al., 2021; Hehua et al., 2017), autism spectrum disorder (Liu et al., 2023), or neurodevelopmental skills (Castagna et al., 2022). To improve our understanding of the life-course health consequences of ambient air pollution exposure, focusing on prenatal exposure is important. However, disentangling the effect of prenatal and postnatal exposure holds multiple challenges, including the possibility of prenatal and postnatal air pollution levels being highly correlated (Aguilera et al., 2013) and the challenge of accounting for different periods of susceptibility throughout a child's life course. Associations with prenatal air pollution exposure might wane over time as associations with childhood exposure become relatively more important. Future research could explore these challenges, for example by investigating effect modification by postnatal ambient air pollution levels, effect modification by the child's age, or a potential dose response relationship with cumulative pre- and postnatal exposure.

The included studies share several limitations which hinder comparison and preclude more definitive conclusions about an association between prenatal exposure to ambient air pollution and LRTIs. Firstly, accurate individual-level exposure estimates need to account for the high spatial variability of some air pollutants (e.g., NO_2) (Karner et al., 2010). As reflected in the OHAT risk bias ratings, some studies used methods which are likely to be inappropriate to capture this variability (e.g., questionnaires or regional/district average concentrations). Secondly, not all included studies clearly distinguished between indoor and outdoor pollution, and we included a study using personal environmental monitoring samplers which would have captured indoor as well as outdoor pollutants (Jedrychowski et al., 2013). Thirdly, the heterogeneity in exposure and outcome assessment reduced comparability across the studies and prohibited a meta-analysis. In terms of air pollution assessment, the studies varied with regards to the pollutants investigated, the data sources and methodologies used (e.g., personal low-cost monitors, modelled data, and observed data), and exposure operationalisation (i.e., continuous or categorical). LRTI case definitions varied with regards to the types of infection and level of severity assessed, and only three studies extracted outcome information from medical record (Belachew et al., 2024; Goshen et al., 2020; Lu et al., 2021; Yang et al., 2023). The other studies relied on caregiver reports which could have led to recall bias. Lastly, there was heterogeneity with regards to covariates included in the adjusted models. For example, only four studies included a variable capturing exposure to ambient air pollution postnatally (Jiang et al., 2018; Liu et al., 2022; Lu et al., 2023; Soh et al., 2018). Postnatal exposure to ambient air pollution is a known risk factor of childhood LRTIs (Ibrahim et al., 2021). Consequently, there could be residual confounding in studies which have not adjusted for important confounders, such as postnatal exposure to ambient air pollution.

With regards to the methods of our systematic review, focusing exclusively on lower (i.e., vs. upper) respiratory tract infections and ambient (i.e., vs. household) air pollution may have limited the number of studies identified and contributed to the scarcity of evidence identified from low- and lower-middle income. In low- and middle-income settings, cooking with solid fuels is more common and household air pollution therefore a particular concern (World Health Organization, 2023). Furthermore, we adopted an intentionally wide exposure definition including proxies such as self-reported traffic density. While this allowed us to present a broad overview of studies related to our research question, it has also introduced additional heterogeneity. We further acknowledge the exclusion of grey literature as well as the absence of an assessment of the certainty of evidence as a limitation of our approach. Inclusion of grey literature can reduce the risk of publication bias, however, we did identify various studies reporting non-significant associations. Assessing the certainty of evidence is generally recommended (Whaley et al., 2020), but the application of existing tools has been found to be challenging in the context of environmental health research and authors have called for the development of modified tools (Boogaard et al., 2023). Despite these limitations, this systematic review advances the field by offering the most comprehensive summary of the existing evidence on prenatal exposure to ambient air pollution and LRTIs to date. Previous literature reviews have included some work on the association evaluated in this systematic review (Yadav and Pacheco, 2023), but this review identified a larger body of literature and is the first based on a systematic search strategy.

5. Conclusion

Given the small number of existing studies, their poor geographical representation, the considerable differences in their methodology, and concerns around bias (including residual confounding, e.g. by postnatal ambient air pollution exposure), the current evidence base is insufficient to establish an association between prenatal ambient air pollution exposure and LRTIs during childhood and adolescence. In the face of the observed heterogeneity across studies, there is need for more detailed and transparent reporting of the methods used (including exposure/outcome assessment, analysis strategies, and choice of covariates) as well as the rationale guiding these method choices. This would be a first step towards establishing best practice and standards.

Since many populations, mainly in low- and middle-income countries, continue to face unsafe levels of air pollution (World Health Organization, 2021), we should aim to further advance our understanding

of the long-term impacts of prenatal exposure to air pollution on health. The increasing availability of satellite data offers an opportunity to expand research to settings without air pollution monitoring stations (Holloway et al., 2021). Moreover, future research should aim to clarify how (i.e., underlying biological pathways), when (i.e., trimester-specific effects), and for whom (e.g. effect modification by maternal characteristics) prenatal exposure to ambient air pollution leads to the greatest health risks.

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CRediT authorship contribution statement

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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