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Outdoor air pollution and near-fatal/fatal asthma attacks in children: A systematic review

Deepa Varghese MBChB^{1,2}  | Kathryn Ferris MBBCh, BAO^{2,3} | Bohee Lee PhD^{2,4} | Jonathan Grigg MD⁵ | Hilary Pinnock MD² | Steve Cunningham PhD¹

¹Department of Child Life and Health, University of Edinburgh, Edinburgh, UK

²Asthma UK Centre for Applied Research, Usher Institute, University of Edinburgh, Edinburgh, UK

³Wellcome-Wolfson Institute For Experimental Medicine, Queen's University Belfast, Belfast, UK

⁴National Heart and Lung Institute, Imperial College London, London, UK

⁵The Blizard Institute, Queen Mary's University, London, UK

Correspondence

Deepa Varghese, MBChB, Department of Child Life and Health, Royal Hospital for Children and Young People, 50 Little France Crescent, Edinburgh EH16 4TJ, UK.
Email: deepa.varghese@ed.ac.uk

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Abstract

Background: Globally, observational studies have demonstrated an association between high levels of air pollution and asthma attacks in children. It remains unclear whether and to what extent exposure may be associated with increased near-fatal/fatal attacks.

Objective: To systematically review the evidence for an association between ambient outdoor air pollution and fatal and/or near-fatal asthma (NFA).

Methods: Following Cochrane methodology, we searched MEDLINE, EMBASE, Web of Science, Scopus, and Open Grey electronic databases for studies reporting the association of fatal/NFA and air pollution (particulate matter [PM], sulfur dioxide, nitrogen dioxide, black carbon and ozone [O₃]) in children. NFA was defined as requiring intensive care unit (ICU) management.

Results: Two reviewers independently screened 1358 papers. A total of 276 studies identified asthma attacks related to air pollution, 272 did not meet inclusion criteria after full-text review. Four observational studies described fatal/NFA, of which three addressed NFA. PM_{2.5} (per 12.5 µg/m³ increase) and O₃ (per 22 ppb increase) were associated with NFA in one study (PM_{2.5}, relative risk: 1.26, confidence interval [CI] [1.10–1.44]), O₃ (1.19 [1.01–1.40]). PM₁₀ was associated with ICU admission in the context of thunderstorm asthma. Elemental carbon was associated equally with NFA that did not require an ICU admission (*p* = 0.67). Studies of fatal asthma including children did not demarcate age within the analysis.

Conclusions: Ozone and PM_{2.5} have been associated with NFA in children but synthesis is limited by the paucity of studies and methodological heterogeneity. Poor reporting of severities of asthma attacks hinders the assessment of whether outdoor air pollution is associated with an increased number of NFA/fatal attacks in children.

KEYWORDS

asthma, outdoor air pollution

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1 | INTRODUCTION

Asthma affects over 300 million people globally. An asthma attack occurs when a trigger such as a virus, airborne allergens or air pollution causes an inflammatory response resulting in bronchoconstriction of small airways. Asthma attacks range in severity from mild to fatal. Between 2001 and 2011, there were 13,749 deaths attributed to asthma in the United Kingdom, 265 of which were in children.¹

There is a significant body of evidence examining the relationship between air pollution and respiratory health. Air pollution has been associated with recurrent respiratory infections,^{2,3} reduced lung function in childhood² and a higher frequency of childhood asthma following exposure in early infancy.³⁻⁵ Compared to adults, the impact of air pollution in children is considered greater for several reasons: (1) smaller airway diameter leading to higher propensity for airway blockage from larger particulate matter (PM),⁶ (2) length of time in playgrounds and outdoor activities is likely to be greater,⁵ (3) increased respiratory rate and preferential mouth breathing result in greater inhalation and deposition of pollutants,^{7,8} and (4) developing lungs are more sensitive to chemical and oxidative stress.⁹

Air pollution is an umbrella term for chemicals and particles which contaminate the atmosphere,¹⁰ some of which can cause harm when inhaled. Common components of outdoor air pollution include waste products of industrial combustion and PM from industry and natural sources. The World Health Organization (WHO) recognizes PM, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon monoxide (CO), and ozone (O₃) as the most significant outdoor air pollutants negatively impacting health.¹¹ Sulfur dioxide is produced from crude oil and coal combustion.¹² Nitrogen dioxide is derived from exhaust and car/vehicle fumes. PM can be any airborne particulate of a measured diameter (micrometers) and consists of primary and secondary components. Primary components include sea salt, elemental or black carbon, trace metals and mineral components,¹³ secondary components include sulphate, nitrate, water, and organic carbon.¹³ PM is further categorized by diameter size, separated into PM_{≤2.5}, PM_{2.5}, and PM₁₀.

Air pollutants are suspected to contribute to asthma symptoms in different ways. Larger particles can physically obstruct and aggravate airways at bronchiole level while smaller particles (PM_{2.5} and PM_{<2.5}) are able to enter the bloodstream across the alveolar-capillary membrane⁶ and can trigger an inflammatory cascade resulting in acute bronchospasm.⁶ Possible mechanisms have also been suggested describing the causation of asthma from air pollution including oxidative stress, airway wall remodeling, upregulation of inflammatory pathways, and enhancing respiratory sensitization to allergens.^{14,15}

Our aim was to perform a systematic review to determine if severe near-fatal asthma (NFA) and fatal asthma attacks are associated with outdoor air pollution in children and young people.

2 | METHODS

This systematic review was registered on PROSPERO (CRD420223-17704) and Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (Supporting Information: Table S1) completed according to Cochrane methodology.¹⁶

2.1 | Information sources and search strategy

Electronic databases were accessed on 8 November 2022. MEDLINE and EMBASE (via OVID), Scopus, Web of Science, Central, and Open Grey were searched for relevant articles. Forward and backward citation searching was carried out. Existing terms describing severe asthma attacks 'critical asthma' and 'status asthmaticus' were included in the search strategy. We recognize that patients presenting to front-line services (general practitioner, emergency department) or hospital admission may present with milder symptoms which deteriorate to require intensive care or result in a fatal attack. To ensure all attacks of interest were captured, search terms were broad (Supporting Information: Table S2) to encompass all severity and presentations of acute attacks in children related to air pollution.

2.2 | Study selection and inclusion criteria

The primary outcome was the association of near-fatal and fatal attacks with air pollution exposure. Cohort, case-crossover, and case-control studies were included. To examine the literature for acute asthma attacks, children and young people presenting with, or receiving treatment for an asthma attack were included. An age range of 2-18 years was selected to exclude patients with other wheezing illness such as bronchiolitis. Papers which included adults but had clearly demarcated the relevant pediatric age group in the analysis were included. Air pollutants based on WHO highlighted outdoor air pollutants¹¹ (CO, NO₂, SO₂, PM [any size], O₃), and additionally, black carbon and benzene were examined. Indoor air pollution exposure was excluded. Long-term and short-term air pollution exposure was included if the outcome was an acute asthma attack in any healthcare setting. Extreme weather events examining the relevant air pollutants were included. The language was restricted to English and translated English studies (Table 1—inclusion-exclusion criteria). We relied on the author's description of asthma attacks, authors were contacted if attacks were described as "severe" or "near fatal" without definition. As the terminology for NFA attacks is inconsistent in the literature, the full text of all remaining studies was reviewed for near-fatal and fatal attacks to identify studies for analysis. For the purpose of this review, near-fatal attacks are defined as the management of an acute asthma attack in an intensive care/critical care setting.

TABLE 1 Inclusion and exclusion criteria.

Inclusion	Exclusion
Population <ul style="list-style-type: none"> Children aged 2–18 years treated for an exacerbation of asthma Studies including adults up to the age of 25 if relevant pediatric population (2–18 years) included Studies including pediatric deaths (age 2–18 years) where asthma identified as cause of death or contributed to death 	Population <ul style="list-style-type: none"> Children <2 years where no definitive asthma treatment defined Children treated for other respiratory illness including bronchiolitis, bronchiectasis, recurrent respiratory infection Adults >18 years with occupational wheeze not related to air pollution Chronic obstructive pulmonary disease
Intervention <ul style="list-style-type: none"> Studies must include measurement or measured exposure to of one of the following: Particulate matter (PM), PM_{2.5} PM₁₀, fine PM, coarse PM, ultrafine PM, ozone (O₃), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), carbon monoxide (CO), benzene, black carbon 	Intervention <ul style="list-style-type: none"> Indoor air pollution exposure Animal models/studies Extreme weather related outdoor air pollution if resulting in increased particulate matter (any size)
Comparison <ul style="list-style-type: none"> Control group in defined geographical areas of low levels of outdoor air pollution Control group observed over specified time period with low levels outdoor air pollution Control group from population with measured minimal exposure to high levels of outdoor air pollution 	Comparison <ul style="list-style-type: none"> For randomized control trials no clear control group without measured/defined area of low level or no outdoor air pollution
Outcome <ul style="list-style-type: none"> Fatal or near-fatal asthma exacerbation Intensive care management of acute asthma attack Primary care review, hospital or emergency call out or attendance requiring escalation intensive care or invasive ventilation, resuscitation or fatal attack 	Outcome <ul style="list-style-type: none"> Subsequent development of asthma postexposure Asthma exacerbations not related to acute exposure Escalation in chronic asthma treatment postexposure to high levels of outdoor air pollution
Study design <ul style="list-style-type: none"> Randomized control trials Case control studies Case cross over trials Cohort studies Grey literature 	<ul style="list-style-type: none"> Editorials, letters to editor Review articles Opinion pieces
Language <ul style="list-style-type: none"> Published studies in English language Translated into studies with asthma, wheeze and severity of attack clearly defined 	

2.3 | Data extraction

Results were screened using the Covidence online platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Once duplicates were removed, two reviewers (D. V. and K. F.) independently screened the title and abstracts to identify studies reporting air pollution and acute asthma exacerbations in children. Any conflicts that could not be resolved by discussion were screened by a third reviewer (B. L.).

2.4 | Quality assessment and bias

To assess study bias, an adapted quality scale used by Mustafić et al. for the assessment of air pollutants' impact on

myocardial infarction was used.¹⁷ This tool evaluated three components (the validation of MI occurrence [0–1 point], the quality of air pollutant measurements [0–1 point], and the extent of adjustment for confounders [0–3 points]). We have adapted this to review NFA and fatal asthma attacks for the purpose of this review. We have chosen to define an NFA attack as intensive care admission however to reflect and acknowledge that criteria for intensive care admission may vary depending on each hospital, 1 point was awarded if indication for intensive care admission was stated and included the escalation of management to invasive ventilation. A fatal attack was awarded 1 point if the cause of death was registered as asthma. Air quality measurements and extend of confounders (0–3 points) were awarded 0–1 point as per similar criteria set out by Mustafić et al.¹⁷ (Table 3)

3 | RESULTS

After duplicates were removed, 1358 studies were screened for relevant air pollutants and asthma attacks in children, of which 276 studies met the criteria for a full-text manual review. The majority of studies were excluded ($n = 217$ of 272, 80%) because the severity of

asthma attack was not clinically described and could not be determined to the granularity of NFA (intensive care admission) or fatal asthma attack (Table 2). Four studies identified cases of fatal and NFA in children (see Figure 1). Three studies addressed NFA attacks (defined as intensive care management) and one study presented a case series of fatal and near-fatal attacks in the event of

TABLE 2 Excluded papers.

Reason for exclusion after full text review	Number of papers	
Did not identify a fatal or near-fatal asthma attack	232	
Incorrect outcome (acute asthma attack not addressed)	14	
Publication not translated to English	9	
Adult population (children not demarcated in analysis)	10	
Incorrect intervention (outdoor air pollutant exposure not addressed)	6	
Unable to obtain full text (abstract only)	1	
Total	272	
Papers excluded as severity not defined	Number	Percentage of excluded papers, %
Severity addressed but fatal/near-fatal attack not included	15/232	6
Use of ICD code or severity not defined (inc systematic reviews)	217/232	94

Abbreviation: ICD, International Classification of Disease.

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources

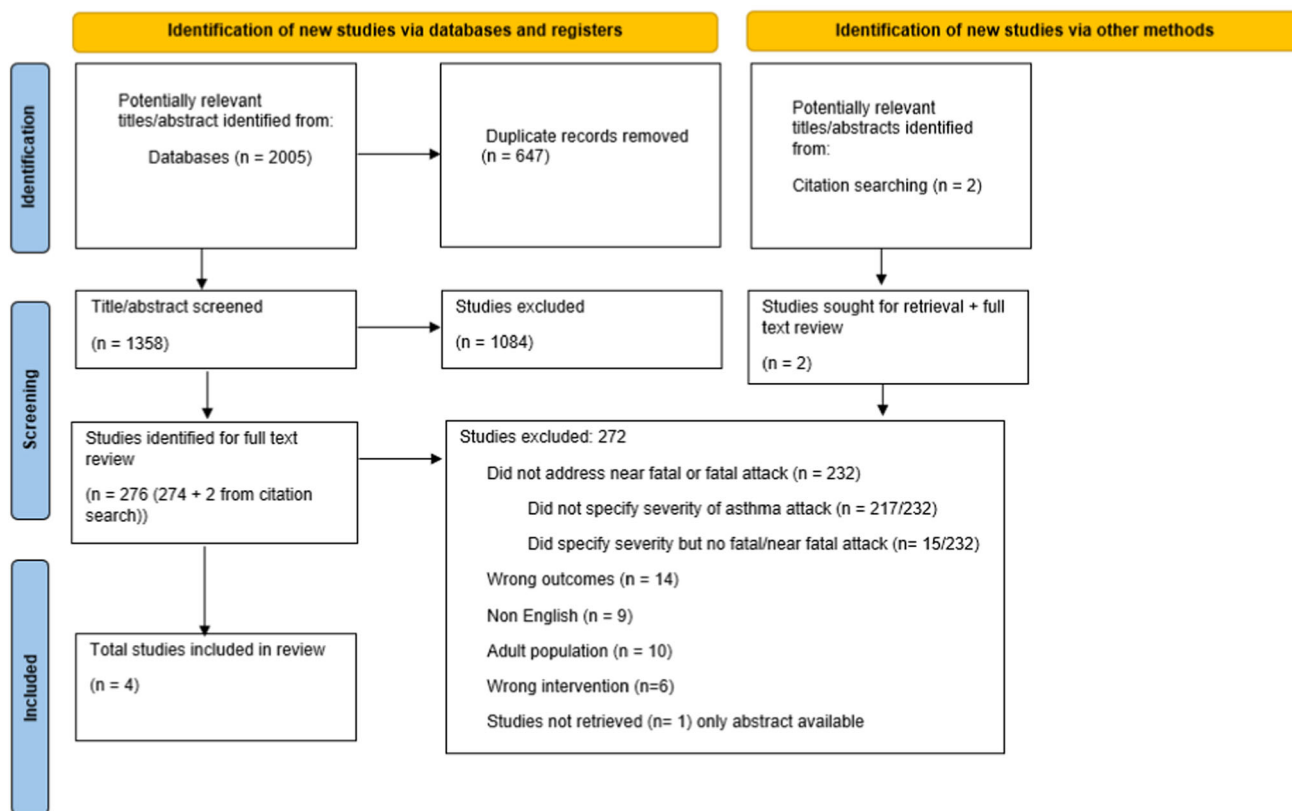


FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-analysis Protocol results. Adapted from: Page et al.²¹ [Color figure can be viewed at wileyonlinelibrary.com]

thunderstorm asthma. Although three studies identified intensive care admissions for NFA, only one study¹⁸ was found to examine air pollutants as an exposure. The other two studies^{19,20} identified included air pollutants as part of a wider analysis of social deprivation and asthma admissions to intensive care. All identified studies were observational. Using the modified scoring from Mustafic et al.,¹⁷ the quality of studies assessed can be viewed in Table 4. Studies scoring 3 in any category were deemed of high quality, low quality if 0 in two categories, and intermediate for any other score (see Table 3).

3.1 | Near Fatal Asthma attacks

The only study that focussed on the impact of air pollutants and NFA,¹⁸ reported intensive care unit (ICU) asthma admissions between April and August in relation to two air pollutants, ozone and PM_{2.5} (see Table 4). Over a 7 year period, 74 hospitals were included in the study, with participants included if a diagnosis of asthma was coded on hospitalization and coded as having an ICU admission or intubation or ventilation. Air pollution data was gathered from national data²² (Table 5). Pollution data was adjusted for weather (humidity and temperature) and seasonal temporal trends. The study found the relative risk of ICU admission per interquartile increment of PM_{2.5} (12 µg/m³) and ozone (22 ppb) was more significant in children aged 6–18 years compared to adults (PM_{2.5} relative risk [RR]=1.26 [confidence interval: 1.10–1.44] and ozone RR=1.19 [1.01–1.40]). This risk of ICU admission was noted at an average lag of 0 and 1 day¹⁸ suggesting increased risk with short-term exposure. Long-term exposure (>7 days) was not examined by this study.

McDowell et al.¹⁹ and Grunwell et al.²⁰ both examined air pollution within the analysis of social deprivation. As such, relative risk was not calculated for specific air pollutants.

McDowell et al.¹⁹ examined Elemental Carbon Attributed to Traffic (ECAT) measured using land use regression models from Cincinnati

Children's Allergy and Air Pollution Study. They observed no difference between ICU admission and non-ICU group admission ($p=0.67$) in ECAT levels above the median (values not stated).¹⁹ Grunwell et al.²⁰ identified NFA from hospital electronic records in children admitted to pediatric ICU. Records were examined for a diagnosis of "status asthmaticus." Air pollutants were not separated for the analysis, air pollution data were combined with measures for education, health and environment, and social and economic factors to create a Childhood Opportunity Index (COI) as a marker of social vulnerability. The COI data on air pollution was obtained from the Centres for Disease Control and Prevention using modeled data from 2010 to 2014.^{25,26} Levels of ozone and PM_{2.5} were similar in both groups.²⁰

3.2 | Weather events

Darvall et al.²³ describe two pediatric cases requiring ICU admissions for asthma in a case series of 35 adult and pediatric patients exposed to elevated PM_{2.5} and PM₁₀ after a thunderstorm in 2016.²³ This was the largest event of thunderstorm asthma that has been described globally. This unique event resulted in 3460 patients seeking medical consultations and resulted in 9 deaths. Confounding factors including humidity and baseline medication use were considered. The study noted elevated levels of PM₁₀ (µg/m³) > 97th percentile for a month and airborne grass pollen ≥ 100 grains/m³. These levels however had been previously documented on other dates within the same year. Pediatric cases were not separated in the analysis.

3.3 | Fatal attacks

Fatal attacks were described by three papers assessed for eligibility by full-text review. Each paper included all age ranges, children were

TABLE 3 Modified validity score.¹⁷

	0	1	2	3
Definition of near-fatal asthma/fatal asthma (0–1)	0 points if ICU admission criteria were not defined by invasive ventilation	1 point was awarded if the indication for intensive care admission was stated and included the escalation of management to invasive ventilation		
Air pollutant measurements	0 points if measurement frequency was not stated or if >25% of data missing	1 point if measurement frequency was stated and <25% of data missing		
Adjustment of cofounders	0 points if no adjustment is made for long-term trends or seasonality or temperature	1 point if only these <3 adjustments have been made	2 points if additional adjustment was made, either for humidity or weather event	3 points if adjustment had been made for seasonal viral infection, atopy, familial smoking

TABLE 4 Data extraction table and validity.

Author	Near fatal/fatal and fatal	Year (study period)	Location	Setting	Study type	Population	Air pollutant	Lag time	Comparison	Outcome	Pollutant measure quality score (0–1 point)	Diagnosis of near fatal/fatal asthma (0–1)	Adjusted quality score (0–3 points)	
														Intervention
Darvall et al. ²³	Near-fatal and fatal	2016 (2 days)	Australia	Intensive care	Retrospective multicenter observational study	Patients with asthma admitted to intensive care	Age 9 and 12 years (n = 2) Number of patients 2	PM _{2.5} ≤ 2.5 PM ₁₀ µg/m ³	2 days	Annual intensive care admissions	Intensive care admission (all cause)	1	0	2
Silverman and Ito ¹⁸	Near fatal	2010 (1999–2006)	America	Intensive care	Time series analysis	Pediatric asthma admissions	Age 6–49 years (>6 and 6–18 grouped) Number of patients 6008	Ozone (22 ppb per IQR change) PM _{2.5} (12.5 µg/m ³ per IQR change)	Average 0–1 day	Non ICU admissions	Effect of age on air pollution risk for admission with very severe asthma	1	1	2
McDowell et al. ¹⁹	Near fatal	2016 (enrolled August 2010 to October 2011)	America	Intensive Care	Prospective Cohort Study	Pediatric asthma admissions	Age 1–18 years Number of patients 771 (160 ICU admissions)	Black carbon	Not stated	Non intensive care admissions	Intensive care admission for severe asthma	1	0	0
Grumwell et al. ²⁰	Near fatal	2022 (2015–2019)	America	Intensive Care	Retrospective cohort	Pediatric intensive care	Age 6–17 years Number of patients 4425 (1705 PICU admissions)	PM _{2.5} µg/m ³ ozone	Not stated	Not stated	Intensive care readmissions for severe asthma	0	0	0

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PICU, pediatric intensive care unit; PM, particulate matter.

TABLE 5 Air pollutants.

Reference	Source	Air pollutants							Units	Meteorological/other adjustment		
		PM2.5	PM10	Ozone	Black Carbon	NO ₂	SO ₂	CO				
Darvall et al. ²³	Air quality monitoring stations (state)	✓	✓						Hourly Number of sites not stated	None	PM2.5 µg/m ³ PM10 µg/m ³	Temperature Humidity Wind
Silverman and Ito ¹⁸	US Environmental Protection Agency Air Quality System	✓		✓					24 h average values (PM2.5) 8 hourly ozone 24 sites	Day 0 and 1	PM2.5 µg/m ³ Ozone—ppb	Temperature Humidity Day of the week Over dispersion
McDowell et al. ¹⁹	Cincinnati Childhood Allergy and Air Pollution Study land use regression model—24 sites				✓				Annual measurement 4–5 sites over different seasons Sites referenced ^a	Not stated	µg/m ³	Distance from air pollution source (location relative to wind direction ^b)
Grunwell et al. ²⁰	National Environmental Public Health Tracking Network, Centres for Disease Control and Prevention. Modeled data combining Air Quality System repository of ambient air quality data (e.g., National Air Monitoring Stations/State and Local Air Monitoring Stations and simulated PM2.5	✓		✓					Annual (data from 2010 and 2014) 8 hourly ozone (data from 2011 and 2014) Sites not stated	Not stated	PM2.5 µg/m ³ Ozone—ppb	Not stated

Abbreviation: PM, particulate matter.

^aSites referenced in Ryan et al.²⁴

^bAirborne allergens, home tobacco smoke exposure, atopy, gender, and financial hardship were recorded as part of the cohort—no separate air pollution analysis was carried out.

not demarcated in analysis or reporting. All corresponding authors were contacted to ascertain if analysis on pediatric age could be attempted. None of the contacted authors responded.

3.4 | Air pollutants

Researchers used inconsistent average time periods for the assessment of air pollution data across the studies (see Table 5). Exposure periods/lag times were not given for two of the studies addressing near-fatal attacks.^{19,20} Grunwell et al.²⁰ used modeled data which is commonly used in the assessment of air pollution levels, was historical data from 2010, 2011, and 2014 (study period 2015–2019).

The most commonly studied air pollutants were ozone and PM_{2.5}. No included studies assessed NO₂ or SO₂ or considered these or other air pollutants in a combined multipollutant impact. Nitrogen dioxide and sulfur dioxide were included in studies of fatal asthma, though data for children could not be extracted as age-related reporting was not provided or available via authors.²⁷

3.5 | Ages

All three near-fatal studies^{18–20} included children aged 5–18 years (Table 4). McDowell et al.¹⁹ also included children <5 years without stratifying age groups and as a result children with other similar wheezing conditions such as bronchiolitis may have been included in their analysis.

3.6 | Heterogeneity of studies

The small number of heterogeneous studies precluded statistical synthesis and limited reporting to a description of the studies. There was a high degree of clinical heterogeneity as a result of differing methodologies (Table 4). The heterogeneity of the study design did not allow a meta-analysis to be performed, limiting any conclusions that could be drawn from the studies identified. Studies were observational and measurement of pollution exposure differed greatly from study to study. Without specified time periods for exposure related to the asthma attack and consistent control groups in all studies, estimation of exposure effect was not possible. Study heterogeneity in observational studies examining air pollution may be expected due to the range of possible study designs and differing methods of measuring air pollutants (dependent on local monitoring stations).²⁸

3.7 | Defining the severity of attacks

This review has identified that while there is a substantial evidence base considering the association of an asthma attack and air pollution

in children ($n = 232$ of 272 excluded—see Figure 1), the evidence considering the severity of asthma attack in relation to air pollution is far more limited ($n = 4$). Of the 232 papers excluded, 217 had not specified whether a near-fatal or fatal attack occurred (see Table 2). Papers frequently addressed “hospital attendance,” “emergency visit,” or “hospital admission” but did not specify if these events resulted in a fatal or near-fatal attack. Children presenting to hospital with acute asthma can present with mild, moderate, severe or near-fatal/fatal episodes and very few papers ($n = 15$, see Table 2) defined this. Within the 217 that did not define severity, 147 used the International Classification of Diseases code “asthma” to identify presentations and patients (see Table 2).

4 | DISCUSSION

4.1 | Principal findings

One of the key findings in this review is the almost absent reporting of the degree of attack severity in patients admitted to the hospital with an asthma attack ($n = 217$ of excluded papers—see Table 2). Consequently, near-fatal and fatal attacks may have occurred but were not reported. Without this key information, conclusions on the severity of asthma attacks related to air pollution in children admitted to hospitals are not possible. While many studies demonstrated an increase in the number of presentations with an acute attack, without quantifying the severity it is not possible to determine if more severe attacks are proportionally increased in association with high levels of outdoor air pollution. Potential reasons for the exclusion of these data may include (1) NFA and fatal asthma attacks are infrequent, (2) the use of diagnostic coding to identify attacks which limits the ability to identify the severity in those admitted to the hospital. The use of diagnostic codes allows the identification of cases but loses details such as severity.

4.2 | Common themes

4.2.1 | Social deprivation

A common theme in the two papers addressing NFA was the relationship between air pollution and social deprivation. McDowell et al.¹⁹ and Grunwell et al.²⁰ both examined air pollution as part of environmental exposures related to socioeconomic status. Air pollution exposure was not a primary exposure in either study. As a result, neither study presented lag times or comparative periods of air pollution levels. This explains our inability to draw conclusions on the specific impact of air pollution on asthma from these two studies. Previous reports from the United Kingdom have shown a correlation between ICU admissions and deprivation,²⁹ highlighting the need for further research exploring the interrelationship between deprivation and air pollution.

4.2.2 | Air pollutants

In studies reporting a relationship between air pollutants to the severity of asthma attacks, there was varied reporting of pollutants, with ozone and PM being the most commonly reported. Standardized reporting of the air pollutants measured, duration of measured exposure (lag time), and average value (annual or 24 h) and consistent reporting of the spread of the air pollution data in future studies would allow better synthesis of data. The use of retrospective air pollution data has benefits as is often readily available; however, it could be considered as a limitation when applied to an acute asthma attack which is likely to be attributed to air pollution levels in the days leading up to the acute attack.

Without experimental conditions, the individual impact of singular air pollutants is difficult to determine. The combined effect of multiple air pollutants should be acknowledged and considered when interpreting the effect of air pollution on asthma attacks. For example, PM can be generated from road vehicle tyres in addition to vehicle fuel combustion waste products such as NO₂. Both are associated with asthma attacks in children. Examining one or another in isolation in relation to an acute asthma attack should acknowledge the potential impact of multiple air pollutants. Similarly, the relationship between airborne allergens as potential contributing factors for asthma attack triggers asthma attacks should also be considered. High pollen counts have been associated with weather phenomenon such as thunderstorms which as shown by Darvall et al.²³ also generate high levels of PM. Separate analysis of individual pollutants may misrepresent any cumulative effect of exposure.

4.2.3 | Exposure duration

The relationship between acute exposure and attacks was demonstrated by the significant weather event observed by Darvall et al.²³ and Silverman et al.¹⁸ None of the studies commented on long-term exposure to air pollution. This is more challenging to quantify in the context of acute attacks. Antenatal, early childhood and infancy exposure to air pollution is associated with an increased asthma prevalence.^{2,30,31} Long-term exposure subsequently raises the questions of 'how often?' and 'how long' was an individual exposed. This can only be truly measured with individual exposure time and must consider confounding factors such as weather, baseline asthma symptoms and intercurrent viral illness. While cohort studies assume individual exposure to outdoor air pollutants in the days/weeks leading up to the event, true exposure cannot be measured accurately without personal measurement devices.^{32,33} Though it may be useful to estimate individual air pollution exposure, it is not pragmatic or practical in NFA or fatal asthma as such events are difficult to predict.

4.3 | Limitations of the study

There were several limitations to our review. A very small number of papers met our inclusion criteria. Widening the age criteria to include

adults may have resulted in a larger number of included studies but would not have answered our research question which focussed on children. Interpreting the resulting data would be unreliable as children are considered to be more sensitive to air pollutants. We therefore considered inappropriate to measure impact across all ages.

Many studies undergoing full-text review described an admission to the hospital as "moderate" or "severe" asthma attack. These nonstandardized descriptions will not, in the majority of cases, equate to a NFA attack. "Status asthmaticus" and "critical asthma," included within our search terms have inconsistent definitions from a physiological and/or clinical perspective and so are unreliable. To differentiate NFA in this review, intensive care admission was used as a proxy marker of NFA attack. Although this creates a clear definition point, we are aware that using intensive care admission as a marker may have excluded cases that were not managed in intensive care due to resource or/and geographical limitations. In addition, individual units may have different thresholds for admission. This may have reduced the number of papers identified.

Although social deprivation was addressed as a common theme in two of the identified studies, all of the studies were conducted in high-income countries. Of those papers manually screened for near-fatal and fatal events, 188 of the 272 papers screened were from high-income countries. This should be considered when addressing the impact of air pollution on fatal and NFA worldwide.

This review did not comment on the role of indoor air pollutants on asthma attacks however this is a key aspect to consider when evaluating environmental exposures. This has been shown to be particularly relevant in low to middle-income countries where indoor air pollutant sources such as cooking stoves have been associated with poor respiratory health.³⁴

For the purpose of this review, the validity of the studies was assessed using a modified assessment proposed by Mustafic et al.¹⁷ This was further modified to provide a relevant and structured approach to bias assessment for this paper however is not formally validated and is a limitation of this review.

4.4 | Meaning of the study: Possible implications

The association of air pollution with the severity of asthma attacks in children requires further research and vitally, quantification of the association. There is now a growing body of evidence associating air pollution and asthma presentations in children³⁵ and a landmark case in the United Kingdom has now reported that air pollution was a primary factor in the death of a child with a fatal asthma attack.³⁶ This systematic review supports the need for additional data considering whether air pollution may increase the risk of asthma attack severity and possible death from asthma. To ensure clear conclusions can be examined regarding air pollution data in children and young people experiencing NFA and fatal asthma attacks in real-time, datasets with clearly defined pollutant and multipollutant models with adjustments for confounding variables and identifiable air pollution exposure time periods are required.

Such data could provide impetus to the need for cleaner air to improve children's health outcomes, as has been highlighted as a priority in environmental policies in the United Kingdom.³⁷

5 | CONCLUSION

The small number of available studies suggests that outdoor air pollution (specifically ozone and PM_{2.5}) may be associated with NFA. These studies add to the consistent evidence that air pollution is contributing to asthma attacks and its prevalence in children. Clearly defined clinical severity of asthma attacks reported in associated with air pollution should be reported in future studies, to enable the identification of fatal and near-fatal attacks.

AUTHOR CONTRIBUTIONS

Deepa Varghese: Writing—original draft. **Kathryn Ferris:** Writing—review and editing; Methodology. **Bohee Lee:** Writing—review and editing; Methodology. **Jonathan Grigg:** Writing—review and editing. **Hilary Pinnock:** Writing—review and editing. **Steve Cunningham:** Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Deepa Varghese  <http://orcid.org/0009-0005-2177-590X>

REFERENCES

- Mukherjee M, Gupta R, Strachan D, Phillips C, Davies G, Sheikh A. Asthma mortality in the UK and member nations between 2001 and 2011. *Eur Respir J*. 2023;48(suppl 60):PA4584. doi:10.1183/13993003.congress-2016.PA4584
- Gehring U, Gruziova O, Agius RM, et al. Air pollution exposure and lung function in children: the ESCAPE project. *Environ Health Perspect*. 2013;121(11-12):1357-1364. doi:10.1289/ehp.1306770
- Bowatte G, Lodge C, Lowe AJ, et al. The influence of childhood traffic-related air pollution exposure on asthma allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy*. 2015;70(3):245-256. doi:10.1111/all.12561
- Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. *Environ Int*. 2017;100:1-31. doi:10.1016/j.envint.2016.11.012
- Tiotiu AI, Novakova P, Nedeva D, et al. Impact of air pollution on asthma outcomes. *Int J Environ Res Public Health*. 2020;17(17):6212. doi:10.3390/ijerph17176212
- Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet*. 2014;383(9928):1581-1592. doi:10.1016/S0140-6736(14)60617-6
- Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol*. 2005;115(4):689-699. doi:10.1016/j.jaci.2005.01.056
- Bateson TF, Schwartz J. Children's response to air pollutants. *J Toxicol Environ Health A*. 2007;71(3):238-243. doi:10.1080/15287390701598234
- Esposito S, Tenconi R, Lelii M, et al. Possible molecular mechanisms linking air pollution and asthma in children. *BMC Pulm Med*. 2014;14(1):31. doi:10.1186/1471-2466-14-31
- World Health Organisation. *Air Pollution*. World Health Organisation; 2024. <https://www.who.int/health-topics/air-pollution>
- World Health Organisation. *Ambient (Outdoor) Air Pollution*. World Health Organisation; 2022. [https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)
- GOV.UK. Emissions of air pollutants in the UK—sulphur dioxide (SO₂). 2024. Accessed March 28, 2023. <https://www.gov.uk/government/statistics/emissions-of-air-pollutants/emissions-of-air-pollutants-in-the-uk-sulphur-dioxide-so2>
- Air Quality Expert Group, Department for Environment, Food and Rural Affairs; Scottish Executive; Welsh Assembly Government; and Department of the Environment in Northern Ireland. Particulate matter in the UK: summary. 2005. Accessed March 16, 2022. https://uk-air.defra.gov.uk/library/assets/documents/reports/aqeg/Particulate_Matter_in_The_UK_2005_Summary.pdf
- Gowers AM, Cullinan P, Ayres JG, et al. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. *Respirology*. 2012;17(6):887-898. doi:10.1111/j.1440-1843.2012.02195.x
- Pfeffer PE, Mudway IS, Grigg J. Air pollution and asthma. *Chest*. 2021;159(4):1346-1355. doi:10.1016/j.chest.2020.10.053
- Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022)*. Cochrane; 2022. <http://www.training.cochrane.org/handbook>
- Mustafić H, Jabre P, Caussin C, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA*. 2012;307(7):713-721. doi:10.1001/jama.2012.126
- Silverman RA, Ito K. Age-related association of fine particles and ozone with severe acute asthma in New York City. *J Allergy Clin Immunol*. 2010;125(2):367-373. doi:10.1016/j.jaci.2009.10.061
- McDowell KM, Kercksmar CM, Huang B, Guilbert TW, Kahn RS. Medical and social determinants of health associated with intensive care admission for asthma in children. *Ann Am Thorac Soc*. 2016;13(7):1081-1088. doi:10.1513/AnnalsATS.201512-798OC
- Grunwell JR, Opolka C, Mason C, Fitzpatrick AM. Geospatial analysis of social determinants of health identifies neighborhood hot spots associated with pediatric intensive care use for life-threatening asthma. *J Allergy Clin Immunol Pract*. 2022;10(4):981-991. doi:10.1016/j.jaip.2021.10.065
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
- United States Environmental Protection Agency. Air Quality System (AQS). August 1, 2013. Accessed March 15, 2023. <https://www.epa.gov/aqs>
- Darvall JN, Durie M, Pilcher D, et al. Intensive care implications of epidemic thunderstorm asthma. *Crit Care Resusc*. 2018;20(4):294-303.
- Ryan PH, LeMasters GK, Biswas P, et al. A comparison of proximity and land use regression traffic exposure models and wheezing in infants. *Environ Health Perspect* 2007;115(2):278-284. doi:10.1289/ehp.9480
- Noelke C, McArdle N, Baek M, et al. Child opportunity index 2.0 technical documentation. 2020. Accessed Nov 18, 2023. <https://www.diversitydatakids.org/research-library/research-brief/how-we-built-it>

26. Centers for Disease Control and Prevention. National Environmental Public Health Tracking Network. Daily census tract-level PM2.5 concentrations, 2011-2014. Data.CDC.gov. November 27, 2018. Accessed November 16, 2023. www.cdc.gov/ephtracking
27. Zhang Y, Xiang Q, Yu C, Yang Z. Asthma mortality is triggered by short-term exposures to ambient air pollutants: Evidence from a Chinese urban population. *Atmos Environ*. 2020;223:117271. doi:10.1016/j.atmosenv.2020.117271
28. Goodman JE, Petito Boyce C, Sax SN, Beyer LA, Prueitt RL. Rethinking meta-analysis: applications for air pollution data and beyond. *Risk Anal*. 2015;35(6):1017-1039. doi:10.1111/risa.12405
29. Mukherjee M, Cunningham S, Bhuia MR, Lo T-YM, Been JV, Sheikh A. Asthma in paediatric intensive care in England residents: observational study. *Sci Rep*. 2022;12(1):1315. doi:10.1038/s41598-022-05414-5
30. Lu C, Miao Y, Zeng J, Jiang W, Shen YM, Deng Q. Prenatal exposure to ambient temperature variation increases the risk of common cold in children. *Ecotoxicol Environ Saf*. 2018;154:221-227. doi:10.1016/j.ecoenv.2018.02.044
31. Gheissari R, Liao J, Garcia E, et al. Health outcomes in children associated with prenatal and early-life exposures to air pollution: a narrative review. *Toxics*. 2022;10(8):458. doi:10.3390/toxics10080458
32. Koh L, Grigg J, Whitehouse A. Personal monitoring to reduce exposure to black carbon in children with asthma; a pilot study. *ERJ Open Res*. 2021;7:00482-2021. doi:10.1183/23120541.00482-2021
33. Harrison RM. Personal exposure monitoring of particulate matter, nitrogen dioxide, and carbon monoxide, including susceptible groups. *Occup Environ Med*. 2002;59(10):671-679. doi:10.1136/oem.59.10.671
34. Rylance S, Nightingale R, Naunje A, et al. Lung health and exposure to air pollution in Malawian children (CAPS): a cross-sectional study. *Thorax*. 2019;74(11):1070-1077. doi:10.1136/thoraxjnl-2018-212945
35. Zheng X, Ding H, Jiang L, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: a systematic review and meta-analysis. *PLoS one*. 2015;10(9):e0138146. doi:10.1371/journal.pone.0138146
36. Dyer C. Air pollution from road traffic contributed to girl's death from asthma, coroner concludes. *BMJ*. 2020;371:m4902. doi:10.1136/bmj.m4902
37. Royal College of Physicians of London. Every breath we take: the lifelong impact of air pollution. February 23, 2016. Accessed January 20, 2022. <https://www.rcplondon.ac.uk/projects/outputs/every-breath-we-take-lifelong-impact-air-pollution>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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