The impact of outdoor pollution and extreme temperatures on asthma-related outcomes: A systematic review for the EAACI guidelines on environmental science for allergic diseases and asthma

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Abstract

Air pollution is one of the biggest environmental threats for asthma. Its impact is augmented by climate change. To inform the recommendations of the EAACI Guidelines on the environmental science for allergic diseases and asthma, a systematic review (SR) evaluated the impact on asthma-related outcomes of short-term exposure to outdoor air pollutants (PM2.5, PM10, NO_2, SO_2, O_3, and CO), heavy traffic, outdoor pesticides, and extreme temperatures. Additionally, the SR evaluated the impact of the efficacy of interventions reducing outdoor pollutants. The risk of bias was assessed using ROBINS-E tools and the certainty of the evidence by using GRADE. Short-term exposure to PM2.5, PM10, and NO_2 probably increases the risk of asthma-related hospital admissions (HA) and emergency department (ED) visits (moderate certainty evidence). Exposure to heavy traffic may increase HA and deteriorate asthma control

Abbreviations: AHR, airway hyperresponsiveness; AQI, air quality index; CI, confidence interval; CO, carbon monoxide; EAACI, European Academy of Allergy and Clinical Immunology; ECAT, elemental carbon attributed to traffic; ED, emergency department; FEV1, forced expiratory flow in the first second; GDG, guideline development group; NH_3, ammonia; NO_2, nitrogen dioxide; O_3, ozone; OP pesticides, organo-phosphoric pesticides; OR, odds ratio; PEF, peak expiratory flow; PM, particulate matter; Q, question; QoL, quality of life; ROB, risk of bias; ROBINS-E, Risk Of Bias In Nonrandomized Studies-of Exposure; RR, risk ratio; SE, standard error; SO_2, sulfur dioxide; SOF, summary of findings; SR, systematic review; TRAP, traffic related air pollution; WHO, World Health Organization.

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(low certainty evidence). Interventions reducing outdoor pollutants may reduce asthma exacerbations (low to very low certainty evidence). Exposure to fumigants may increase the risk of new-onset asthma in agricultural workers, while exposure to 1,3-dichloropropene may increase the risk of asthma-related ED visits (low certainty evidence). Heatwaves and cold spells may increase the risk of asthma-related ED visits and HA and asthma mortality (low certainty evidence).

KEYWORDS
asthma, extreme temperatures, GRADE, outdoor pollution, systematic review

1 | INTRODUCTION

Asthma is one of the most prevalent chronic diseases and represents a global public health problem affecting over 300 million people worldwide, with an estimated further increase of 100 million by 2025.[1,2] Asthma is a typical environmental-driven disease with exposure to infections, allergens, pollutants, and other environmental stressors significantly increasing the risk of new-onset asthma and of asthma exacerbations or other asthma-related adverse outcomes.[3–7]

Inhalable air pollutants, such as particulate matters (PMs) with an aerodynamic diameter equal to or less than 2.5 μm (PM2.5) and equal to or less than 10 μm (PM10), ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and carbon monoxide (CO), have become recognized as one of the biggest environmental threats to human health, as acknowledged by the most recent World Health Organization (WHO) global air quality guidelines.[8] Other important outdoor pollutants are volatile organic compounds, ammonia, methane, hydrocarbons, black carbon, and ultrafine particles of nanoscale size (less than 0.1 μm). Outdoor air pollutants are emitted by vehicles, heating systems, industry, refineries, thermoelectric power plants, agriculture, etc. They can also be generated by natural phenomena such as fires, volcanic eruptions, dust storms, erosion, etc.[3,5]

Although outdoor air pollution almost always occurs as a mixture, and in combination with other triggers (microbes and/or allergens), air quality is regulated for each individual component.[8] Consequently, observational or intervention studies have been focused on individual pollutants. This is contrast with large epidemiological studies which inherently involve exposure to mixtures of pollutants and other triggers—the exposome.[7] With increasing attention to traffic-related air pollution (TRAP) as the exposure of interest, a shift has occurred away from a focus on individual components of the pollution mixture, and more lately, to the exposomics as provider a risk profile instead of single predictors.[7]

Individual air pollutants have been linked for a long time to asthma exacerbations and other asthma-related adverse outcomes such as loss of asthma control, increased healthcare resource utilization, low lung function, or decreased quality of life (QoL).[4,9–15] Additionally, there is an emerging body of evidence about the influence of TRAP on asthma.[16,17] At high concentrations, such as those noted in megalopolises from developing or low-income countries, air pollutants might have direct irritant and inflammatory effects on airway epithelium and neuroreceptors, but such levels of exposure are rarely reported in developed countries. At the lower concentrations that are more typical in high-income countries, other mechanisms are probably in operation.[18] Specific pollutants can induce airway inflammation (e.g., O_3, NO_2, and PM 2.5) and airway hyperresponsiveness (AHR) (O_3 and NO_2).[4,18–23] Increased oxidative stress (a feature of severe asthma) has been associated with exposures to O_3, NO_2, and PM 2.5.[4,24] Recent data show that the damage to the epithelial barrier initiates innate and adaptive immune responses, microbiome alterations, followed by chronic inflammation.[25–27] *Genetic and epigenetic variation, atopic background, and allostatic responses may explain the differences in how people with the same level of asthma severity and control respond to air pollution exposure, highlighting the need for better understanding of the environmental endotypes of asthma.*[7,28–30]

In addition to the specific chemical characteristics of air pollutants, another key question is whether short-term peak exposures versus time-weighted averages over longer time periods are associated with increased risk of adverse asthma outcomes. Recent evidence points to peak exposures being more important than long-term exposure, although more data are needed to address this question.[31–33]

Several clinical and epidemiological studies have reported an association between exposure to pesticides, AHR and asthma symptoms, although the causal relationship is still under debate.[34,35] In the form of aerosols or gases, pesticides damage the epithelial barrier and stimulate irritant receptors in the airways with neurogenic inflammation that adds to the chronic inflammation in asthma leading to exacerbation or loss of control.[26,34,36] Organophosphorus (OP) insecticides can enhance AHR by disrupting the negative feedback control of cholinergic regulation in the lungs.[34,37,38]

As a direct result of climate change extreme temperatures (heat waves and cold spells) are increasing in intensity, frequency, and duration causing significant stress in all living organisms. The biological impact of extreme temperatures (structural changes, enzyme function disruption, and damage through reactive oxygen or nitrogen species) can be mitigated through adaptive mechanisms such as the generation of heat shock proteins, antioxidants, and others; however, these mechanisms may likely become inadequate with further global warming.[39–41] Extreme temperatures may pose considerable impact on asthma. A recent systematic review (SR) evaluated 111

eligible studies in the qualitative synthesis, and 37 articles were included in the meta-analysis (20 for extreme heat, 16 for extreme cold, and 15 for temperature variations). Synergistic effects of extreme temperatures, indoor/outdoor pollution, and individual vulnerabilities were reported as important triggers for asthma attacks, especially when there is extreme heat or cold. Meta-analysis further confirmed the associations, and the pooled relative risks for asthma attacks in extreme heat and extreme cold were 1.07 (95%CI: 1.03–1.12) and 1.20 (95%CI: 1.12–1.29), respectively.[42]

The aim of this SR and meta-analysis was to synthesize and update the current scientific evidence on the impact of short-term exposure to outdoor air pollution, heavy traffic, outdoor pesticides, and extreme temperatures on the risk of developing new-onset asthma and on asthma-related outcomes. In addition, it assessed the efficacy of interventions to reducing outdoor pollutants. Other components of the exposome such as airborne allergens or viruses were not included, although we acknowledge their reciprocal interaction with the exposures assessed in this SR.

This research was conducted to inform the recommendations enclosed in the clinical care guidelines developed by the European Society of Allergy and Clinical Immunology (EAACI) on the environmental science for allergic diseases and asthma.

2 | METHODS

2.1 | Structured questions and outcome prioritization

The Guideline Development Group (GDG) framed seven clinical questions (Q): (Q1) "Does exposure to outdoor air pollutants impact asthma-related outcomes?"; (Q2): "Does heavy traffic impact asthma-related outcomes?"; (Q3) "Does reduction of outdoor air pollution impact asthma-related outcomes?"; and (Q4): "Does exposure to outdoor pesticides increase the risk of new-onset asthma?"; (Q5) "Does exposure to pesticides impact asthma-related outcomes?"; (Q6) "Does exposure to extreme temperatures increase the risk of new-onset asthma?"; and (Q7) "Does exposure to extreme temperatures impact asthma-related outcomes?". The population was defined as children and adults with asthma for all clinical questions except questions 4 and 6 where the population were healthy children and/or adults. The asthma-related outcomes were prioritized by the GDG using a 1–9 scale (7–9: critical; 4–6: important; and 1–3: of limited importance), as suggested by the GRADE approach. The critical outcomes were severe asthma exacerbations (defined by the occurrence of emergency department [ED] visits, hospital admissions or systemic steroid use), asthma control, and QoL. Important outcomes for were lung function (assessed by the forced expiratory volume in 1 s [FEV1] and/or peak expiratory flow [PEF]), severity of asthma symptoms, and use of asthma rescue medication (Table 1). For questions 4 and 6 assessing the risk of new-onset asthma, the outcomes evaluated were incident asthma, incident recurrent wheezing, and low lung function (all considered of critical importance).

2.2 | Search methodology

Electronic search queries were applied to the following databases: (1) MEDLINE (last search date: June 02, 2022); (ii) EMBASE (June 13, 2022), and (iii) Web of Science Core (June 02 2022). Three search strategies were built—(i) for outdoor pollutants and TRAP (Q1, Q2, and Q3); (ii) for outdoor pesticides (Q4 and Q5); and (iii) for extreme temperatures (Q6 and Q7). Search algorithms were adapted to the requirements of each database (Tables S1A–S1C). Additionally, studies included in previous SRs were reviewed, together with GDG consultation for missing any potential study that could be included.

In particular, the SRs followed the quality criteria as defined by the AMSTAR-2 tool.[43] These criteria require the SR to search on at least two biomedical databases, to explicit report the results and to assess the risk of bias (ROB) of the studies included. A good quality SR on the impact of outdoor pollution (Q1) was identified[44] with reporting concordant with the current SR protocol.

2.3 | Eligibility criteria and selection of studies

This SR included observational studies (cohorts, case–control, ecological, time-series, and case-crossover studies) that either measured exposure to outdoor air pollution at short term (Q1), TRAP (Q2), outdoor pesticides (Q4 and Q5), or extreme temperatures (Q6 and Q7) or interventions that intended to reduce mean daily air pollutants (i.e., below the WHO recommended thresholds) over a geographical area, such as vehicle traffic restrictions, traffic exclusion areas, or confinements (Q3). Studies that measured the change in pollutant concentrations were also included for Q3. For Q5, only studies that used a rigorous definition of cold spells and heatwaves (i.e., a short period of time where the temperature is below the fifth percentile, or above the 95th percentile of the mean temperature distribution across the entire year) were included. For Q4 and Q6, cohort studies were prioritized. Reviews, abstracts, or conference communications not published as full articles in peer review journals, and publications in a language other than English were excluded.

Based on the eligibility criteria, one reviewer screened the results of the primary search based on title and abstract, to identify potentially eligible studies. After initial calibration, two reviewers confirmed eligibility based on the full text assessment of each of the potentially relevant articles. Disagreements were consulted with a third reviewer.

2.4 | Data extraction and ROB assessment

After calibration, one reviewer used a predesigned extraction form for the relevant data from eligible studies. In particular, study design, method used for pollutant measurement, study location and time period, number and age group of asthma patients, exposure definitions/thresholds, assessed outcomes and their definition, and effect estimates and their 95% confidence intervals (CI) were thoroughly

TABLE 1 PE(I)CO questions and prioritization of outcomes for the SR.

	Q1	Q2	Q3	Q4 and Q5	Q6 and Q7
P (population)	Children or adults with asthma	Children or adults with asthma	Children or adults with asthma	Children or adults, with (Q5) and without (Q4) asthma	Children or adults, with (Q7) and without (Q6) asthma
E (exposure) I (Intervention)	Short-term outdoor air pollutants (up to 7 days) measured as the increase of PM2.5, PM10, NO_2, O_3, SO_2, and CO (all pollutants evaluated in separate analysis)	Individual exposure in the local (1 km) or neighborhood (1–5 km) scale, to TRAP or leaving near heavy traffic. Measured as*: 1. TRAP modelled using at least one traffic predictor (e.g., traffic intensity or road density) 2. Indicators based on distance, length of roads, or traffic density	Interventions to reduce emissions of PM2.5, PM10, NO_2, O_3, SO_2, and CO	Pesticides classified by their chemical nature in: • organophosphates • carbamates • organochlorine • pyrethroid • neonicotinoids • microbial pesticides • plant growth regulators • swimming pool treatments	Extreme temperature classified in: • Cold spell (mean temperature under the first, second, third, fourth, and fifth percentiles) • Heatwaves (mean temperature exceeding the 95th, 96th, 97th, 98th, and 99th percentiles of the year-round distribution)
C (comparison)	Exposure to lower levels of air pollutants (difference of 10 μg/m3)	Living in a low traffic area or low/no exposure to TRAP	No intervention	No or low level of exposure	Mean temperature between percentile fifth to 95th
O (outcome)	**Critical:** Severe asthma exacerbation evaluated with emergency department visits or hospital admissions or systemic steroid use Moderate asthma exacerbation Asthma control Quality of life Asthma mortality **Important:** Lung function (FEV1, PEF) Asthma symptoms Use of asthma rescue medication			(Q4 and Q6) **Critical:** Critical: Incident asthma (doctor diagnosed asthma), incident recurrent wheezing (for infants or preschooler children) or lung function (Q5 and Q7) Same as for Q1 to Q3	

Abbreviations: CO, carbon monoxide; FEV1, forced expiratory volume in 1 s; NO_2, nitrogen dioxide; O_3, ozone; PEF, peak expiratory flow; PM, particulate matter; Q, Question; SO_2, sulfur dioxide; TRAP, traffic air pollution.

*Based on exposure framework of the Health Effects Institute.[1]

described. A second reviewer performed a quality control of the data extraction process. Disagreements were consulted with a third reviewer.

One reviewer assessed the ROB of included studies, and a second reviewer performed a quality control of that assessment. Disagreements were solved by consensus. For non-comparative studies assessing exposure to outdoor pollutants, TRAP, pesticides and extreme temperatures, the Risk of Bias In Nonrandomized Studies-of Exposures (ROBINS-E) tool was used for the ROB evaluation.[45] ROBINS-E includes the following domains: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of exposures, (4) bias due to departures from intended exposures, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of reported results. For comparative cohorts, the Risk of Bias In NonRandomized Studies-of Interventions (ROBINS-I) tool was used.[46] The seven items included in ROBINS-I are: (1) bias due to confounding (e.g., time-varying confounding that occurs when the intervention received can change over time, variability in administrative data collection), (2) bias in selection of participants, (3) bias in measurement classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of reported results.

For the assessment of the "bias due to confounding" domain, low RoB was considered for those studies that included ambient temperature and humidity in the analysis for outdoor pollutants exposure, and at least two of the following in the analysis for TRAP exposure: gender, age, race/ethnicity, socioeconomic status, residence distance to the hospital, asthma controller use, and body mass index. In addition to those variables, for pesticide exposure, smoking status, allergic status, atopy, type of work (e.g., agricultural operations, farming activities, etc), and exposure to dust were also considered. For the risk of new-onset asthma following pesticides exposure, maternal allergy was also evaluated as a confounder. For exposure to extreme temperatures, the SR considered a comprehensive evaluation of the risk domain when the study reported on confounding factors such as humidity or aridity, concomitant exposure to air pollutants (e.g., NO_2, O_3, PM10, and PM2.5), and allergens (e.g., pollen).

2.5 | Data synthesis and analysis

Results were described narratively and tabulated as summary of findings (SoF) tables. Risk ratios (RR) and odds ratios (OR) were used as measures of effect. RR and their standard error (SE) or 95% confidence intervals (CI) were extracted from the studies. When the latter was reported, standard techniques were used for calculating SEs. When studies reported OR a "rare-disease assumption" was made, thus OR were considered to approximate RRs.[47] The percentage excess, increment, or change was also recalculated to reflect RR. Estimates such as rate ratios, scaled beta coefficient (linear regression), and correlation coefficients were not included in the analyses.

When possible, a formal quantitative synthesis (meta-analysis) was conducted by pooling estimates of effect across studies using the random effects model using the DerSimonian and Laird method.[48] For analyses based on ≤20 primary studies, the Hartung and Knapp adjustment was used to estimate the 95%CI.[49] To facilitate comparisons across studies, the effects estimates were standardized to a 10 mcg/m^3 increase for all outdoor pollutants evaluated (PM2.5, PM10, CO, SO_2, NO_2, and O_3) and stratified by single day lag (defined as the time distance—in days between the exposure to the pollutant evaluated and the occurrence of the asthma-related outcome). The heterogeneity was assessed using the Higgins' I^2 statistic.[50] When possible, subgroups analyses were performed by age (children [<18 years], adults [≥18–65 years old], and the elderly [>65 years]), asthma severity, air pollutant or pesticide type and ROB. All statistical analyses were conducted with Stata v.15 software.

2.6 | Certainty of the evidence

The certainty (quality) of the evidence was rated for each outcome as moderate, low, or very low, following the GRADE approach. *The evidence was not graded as high certainty as only observational studies were included*. The quality of evidence was evaluated following the standard GRADE domains (ROB, imprecision, inconsistency, indirectness, and publication bias).[51]

3 | RESULTS

Overall, a total of 11,284 individual records were retrieved from databases searches for all questions (Figures 1–3). For Q1, 190 records were selected for full text assessment and 148 studies were included (67 from the previous SR and 81 from the new search) (Tables S2 and S3). For Q2, 41 studies were selected for full text assessment and 12 studies were included[17,52–62] (Table S4). For Q3, 23 studies were selected for full text assessment and 10 studies were included[63–72] (Table S5). For Q4 and Q5, 55 studies were selected for full text assessment and 19 studies were included (15 for Q4 and four for Q5)[35,73–90] (Tables S6 and S7). For Q6 and Q7, 139 studies were selected for full text assessment. For Q6, no study was identified and 16 were included for Q7[91–106] (Table S8). The studies excluded after full text assessment and the reasons for exclusion are displayed in Table S9.

3.1 | Short-time exposure to outdoor air pollutants as a risk factor for adverse asthma-related outcomes (Q1)

3.1.1 | Characteristics of studies included

The SR included 148 studies assessing the effect of exposure to air pollutants in asthma-related outcomes. Most studies were conducted in Europe (26%), China (22%), and the USA (20%). Most studies were either ecological time-series (64%) or case-crossovers (32%), with periods covered ranging from 1 to 5 years in most studies. Only 16% of studies assessed periods longer than 10 years. More than half of

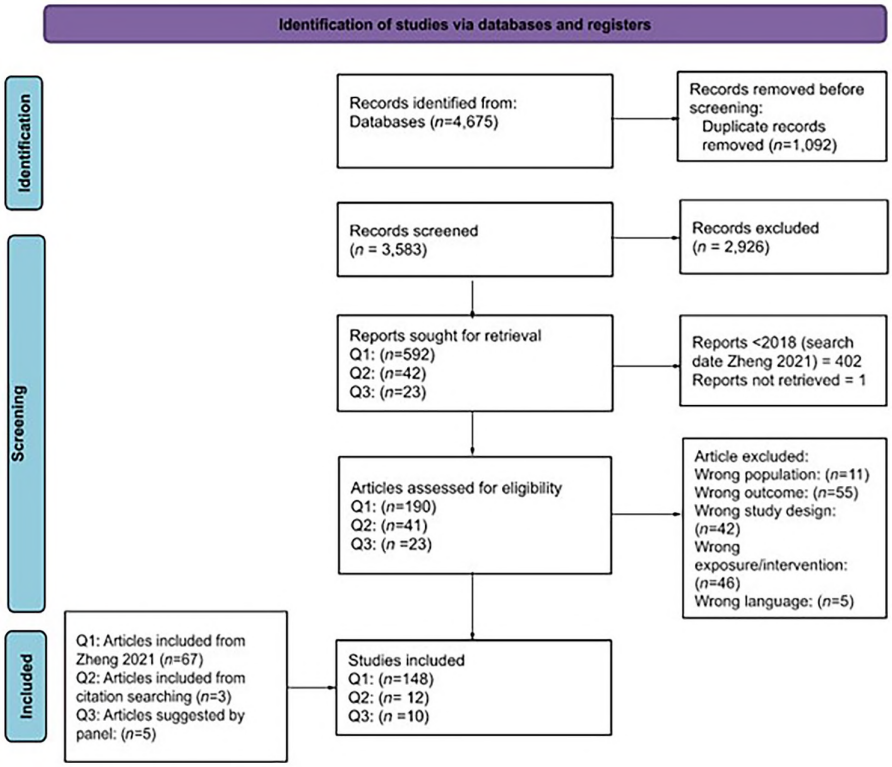

FIGURE 1 Study selection flowchart for air pollutants (CO, O_3, NO_2, PM, and SO_2) and TRAP.

the studies (55%) assessed participants of all age groups, with the remainder assessing either only children (32%) or adults (9%). Table S10 presents a summary of the ROB assessment per domain for the studies included. There were only 14 studies classified as having a low ROB in all assessed domains. The domains most frequently classified as having a high risk of bias were those related to missing data (23%), outcome measurement (20%), and confounding (10%).

All studies assessed either asthma ED visits or hospital admissions with 0–4 lag days following exposure (Tables 2–7). No studies assessing asthma control, asthma-related quality of life, lung function, asthma symptoms, and asthma medication were found.

3.1.2 | Severe asthma exacerbations: asthma-related ED visits

Based on meta-analytical results, an increase in 10 mcg/m^3 of PM2.5 was associated with an increase in asthma-related ED visits, either occurring at the same day (lag 0) (18 studies; RR = 1.012; 95%CI = 1.001–1.023), at lag 1 (i.e., after 1 day) (15 studies; RR = 1.013; 95%CI = 1.004–1.022), lag 2 (14 studies; RR = 1.014; 95%CI = 1.004–1.025), lag 3 (14 studies; RR = 1.023; 95%CI = 1.007–1.039), and possibly 4 days after exposure (Seven studies; RR = 1.016; 95%CI = 0.996–1.037). This results in 452–846 more exacerbations per 100,000 patients. The certainty of the evidence was considered "moderate," except for the association between exposure to PM 2.5 and ED visits 4 days after (low certainty of the evidence) (Table 2, Figure 4).

For the remaining pollutants (PM10, CO, NO_2, O_3, and SO_2), a nonsignificant trend between increased exposure and higher risk of asthma-related ED visits was mostly found. However, evidence was considered either of very low or low certainty (Tables 3–7). The only exception was for the association between O_3 exposure and ED visits at lag 1 (22 studies; RR = 1.008; 95%CI = 1.004–1.012; resulting in 283 more exacerbations per 100,000 patients), for which evidence was considered of moderate certainty.

3.1.3 | Severe asthma exacerbations: asthma-related hospital admissions

Overall, in meta-analytical results, increased exposure to pollutants associated with increased risk of asthma-related hospital admissions. However, the association was not found to be significant for all assessed time lags. The pollutants for which more consistent associations were found were PM10 and NO_2. In detail, for each pollutant, the following increases in exposures were associated with a probable increase in HA (with moderate certainty (Tables 2–7, Figure 5)):

- PM2.5: Increase in 10 mcg/m^3 of PM2.5 measured on lag 3 (25 studies; RR = 1.003; 95%CI = 1.000–1.006); 109 more exacerbations per 100,000 patients.
- PM10: Increase of PM10 measured on lag 1 (21 studies; RR = 1.006; 95%CI = 1.002–1.010), lag 2 (22 studies; RR = 1.008; 95%CI = 1.003–1.013), and lag 3 (21 studies; RR = 1.004; 95%CI = 1.001–1.008) (165–283 more exacerbations per 100,000 patients).

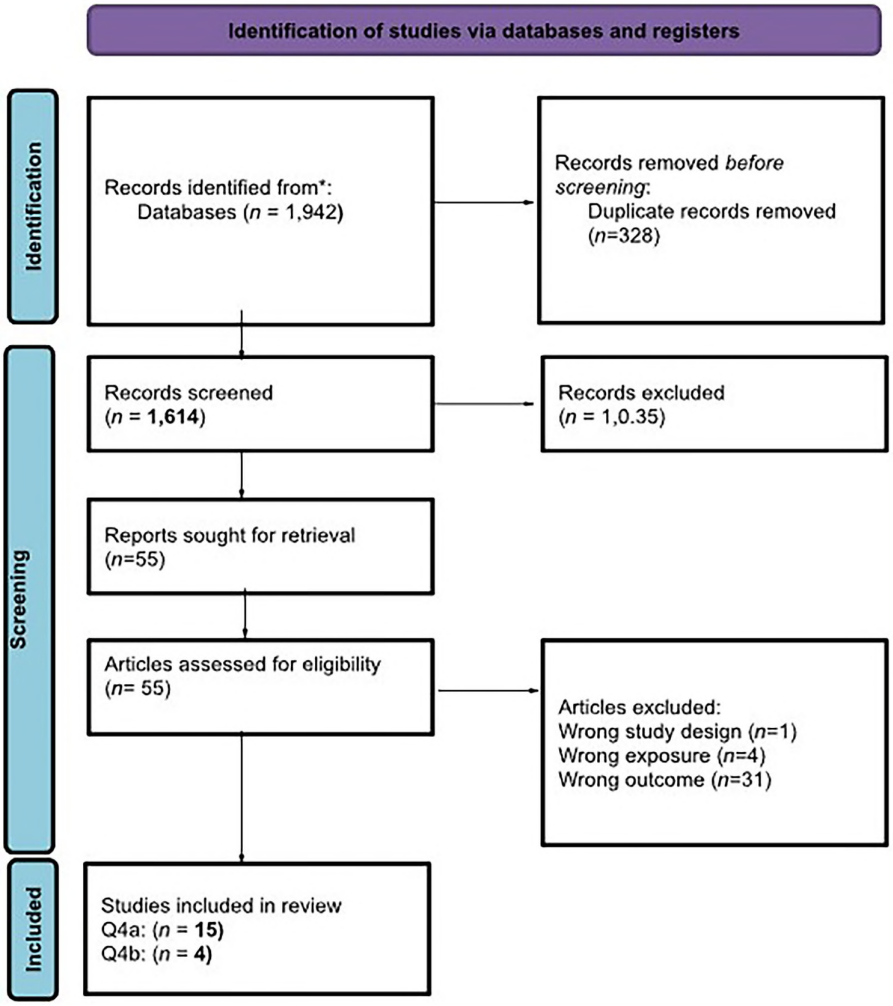

FIGURE 2 Study selection flowchart for pesticides.

- CO: Increase of CO measured on lag 2 (12 studies; RR = 1.014; 95%CI = 1.008–1.021), and lag 4 (10 studies; RR = 1.015; 95%CI = 1.006–1.025) (534–564 more exacerbations per 100,000 patients).
- NO_2: Increase of NO_2 measured on lag 1 (26 studies; RR = 1.003; 95%CI = 1.000–1.006), lag 2 (20 studies; RR = 1.005; 95%CI = 1.002–1.008), lag 3 (16 studies; RR = 1.022; 95%CI = 1.002–1.044), and lag 4 (12 studies; RR = 1.019; 95%CI = 1.004–1.035) (106–826 more exacerbations per 100,000 patients).
- O_3: Increase of O_3 measured on lag 1 (24 studies; RR = 1.014; 95%CI = 1.007–1.021), and lag 2 (22 studies; RR = 1.011; 95%CI = 1.004–1.019) (422–510 more exacerbations per 100,000 patients).
- SO_2: Increase of SO_2 measured on lag 1 (18 studies; RR = 1.020; 95%CI = 1.005–1.036; 740 more exacerbations per 100,000 patients).

The remaining associations, nonsignificant increases in the frequency of hospital admissions were observed, with evidence being classified as being of low certainty.

It was not possible to conduct the subgroup analysis for adult and pediatric population, due to the heterogeneous reporting of the information. Visual inspection of forest plots did neither reveal substantial differences in the magnitude, nor direction of the effect, for the pediatric population compared to the general population.

3.2 | Exposure to heavy traffic-derived pollutants as a risk factor for adverse asthma-related outcomes (Q2)

3.2.1 | Characteristics of studies included

The SR included 12 studies assessing the effect of exposure to TRAP on asthma-related outcomes. Most studies were from USA (75%), and the other two studies were from Australia and Mexico. Only one study had a cross-sectional design, one was a case–control study, and the rest were cohort studies. Most studies evaluated periods between 1 and 5 years (91%), and one had an observation period of 11 years. Two thirds of the studies assessed children, while the remainder assessed either adults (17%) or participants of any age

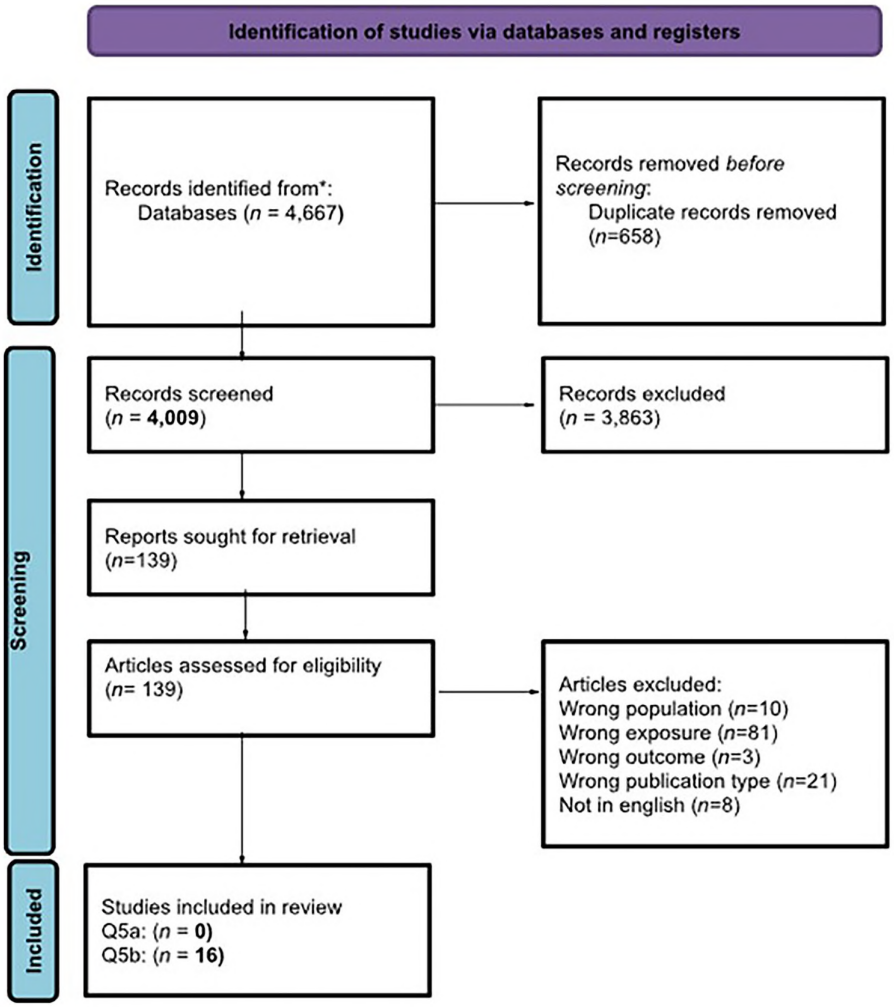

FIGURE 3 Study selection flowchart for extreme temperatures.

(17%). Most studies assessed TRAP exposure based on the distance from the participants' residency to major roads (50%) or TRAP density in a prespecified area around the participant's residency (42%), and only three studies assessed exposure to specific components of TRAP, namely elemental carbon attributed to traffic (ECAT) and NO_2, NOx, and CO. Table S11 presents a summary of the risk of bias assessment per domain. There were only seven studies classified as having a low risk of bias in all domains assessed. There was only one domain for which there was a "high risk of bias" classification (risk of bias arising from measurement of the exposure).

Table 8 presents the summary of findings table for this association. A meta-analysis could not be conducted due to substantial heterogeneity in the exposure assessment and in the method of analysis used to estimate the effect indicators.

3.2.2 | Severe asthma exacerbations (asthma-related ED visits and hospital admissions)

There were two studies in children (with a 12-month follow-up) assessing the association between asthma-related hospital admissions and either exposure to TRAP (OR = 1.4; 95%CI = 0.9–2.2) or proximity to major roadways (OR = 2.45; 95%CI = 1.23–4.89).[17,53] Evidence was considered of low certainty (Table 8).

Exposure to traffic (assessed by proximity to major roads and traffic density) had an unclear impact (very low certainty) on the risk of ED visits in children. However, all point estimates suggested a positive (even if not always significant) association (ORs ranging from 1.07 to 1.24).[17,55,62]

Lastly, traffic exposure assessed with either traffic density or proximity to major roads was associated with a possible increase in asthma exacerbations reported as a composite of asthma-related hospital admissions, ED visits, and repeated outpatient visits both in the general population[59] and in children.[54,56] Evidence was classified as low certainty.

3.2.3 | Asthma control

One study, including patients older than 65 years of age, showed that exposure to TRAP compounds may result in poorer asthma control (low certainty). Specifically, an increase in ECAT concentrations from 0.39 to 0.51 mcg/m^3 was associated with a 0.5 unit increase in the Asthma Control Questionnaire scores.[57]

TABLE 2 Impact of short-term exposure to PM2.5 on asthma exacerbations.

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Baseline risk	Risk difference with a 10 mcg/m^3 increase of PM2.5 (95% CI)
ED Visits—Lag 0	18 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.012 (1.001–1.023)	36,871 per 100,000	+452 per 100,000 (+53 to +856)
ED Visits—Lag 1	15 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.013 (1.004–1.022)	36,871 per 100,000	+ 485 per 100,000 (+163 to +810)
ED Visits—Lag 2	14 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.014 (1.003–1.025)	36,871 per 100,000	+515 per 100,000 (+127 to +908)
ED Visits—Lag 3	14 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.023 (1.007–1.039)	36,871 per 100,000	+ 846 per 100,000 (+270 to +1431)
ED Visits—Lag 4	7 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.016 (0.996–1.037)	36,871 per 100,000	+ 598 per 100,000 (−159 to +1370)
Hospital Admissions—Lag 0	30 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.007 (0.992–1.023)	36,871 per 100,000	+ 272 per 100,000 (−284 to +837)
Hospital Admissions—Lag 1	31 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.006 (1.000–1.012)	36,871 per 100,000	+ 225 per 100,000 (−8 to +460)
Hospital Admissions—Lag 2	31 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.011 (0.997–1.025)	36,871 per 100,000	+ 404 per 100,000 (−94 to +908)
Hospital Admissions—Lag 3	25 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.003 (1.000–1.006)	36,871 per 100,000	+ 109 per 100,000 (+8 to +209)
Hospital Admissions—Lag 4	19 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.002 (0.997–1.007)	36,871 per 100,000	+ 70 per 100,000 (−129 to +269)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; PM, particulate matter RR, risk ratio.

[a] The evidence on the impact of environmental exposures on human health outcomes typically comes from nonrandomized studies (NRS). The risk of bias assessment already considers the limitations of lack of randomization; therefore, all studies within the bodies of evidence will start at the same "High" initial certainty within GRADE regardless of study design.

[b]Although most of the studies adjusted for the major confounders, unmeasured and uncontrolled confounding cannot be ruled out. Outcome measurement was not done with validated classification criteria and uncertain imputation methods for missing values were used in some of the studies.

[c]Unimportant statistical heterogeneity; most point estimates consistently indicate a harmful effect of increasing pollutant. The analysis detected clinically irrelevant differences as statistically significant variability due to large samples and very narrow 95%CI of included studies.

[d]Asthma exacerbations measured as emergency room visits/hospital admissions (for asthma) from administrative data and registries. Details on how asthma exacerbation was measured or accounted were missing. Administrative data and registries may over or under-represent the outcome of interest.

[e]The 95%CI includes beneficial as well as a harmful effect. Even though the relative risk appears to be very small, at a population level even a small effect (beneficial or harmful) may have a relevant impact.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1–exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)–RB.*

TABLE 3 Impact of short-term exposure to PM10 on asthma exacerbations.

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Baseline risk	Risk difference with a 10 mcg/m^3 increase of PM10 (95% CI)
ED Visits—Lag 0	7 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.014 (0.994–1.034)	36,871 per 100,000	+500 per 100,000 (−224 to +1237)
ED Visits—Lag 1	8 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.008 (0.995–1.022)	36,871 per 100,000	+306 per 100,000 (−197 to +816)
ED Visits—Lag 2	7 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.004 (0.994–1.015)	36,871 per 100,000	+160 per 100,000 (−234 to +559)
ED Visits—Lag 3	6 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.008 (0.995–1.021)	36,871 per 100,000	+293 per 100,000 (−187 to +779)
ED Visits—Lag 4	2 observational studies	⨁◯◯◯ Very low[a,b,c,d,e]	RR 1.010 (0.889–1.147)	36,871 per 100,000	+358 per 100,000 (−4084 to +5406)
Hospital Admissions—Lag 0	28 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.002 (0.981–1.024)	36,871 per 100,000	+90 per 100,000 (−685 to +882)
Hospital Admissions—Lag 1	21 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d,e]	RR 1.006 (1.002–1.010)	36,871 per 100,000	+225 per 100,000 (+70 to +381)
Hospital Admissions—Lag 2	22 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d,e]	RR 1.008 (1.003–1.013)	36,871 per 100,000	+283 per 100,000 (+96 to +472)
Hospital Admissions—Lag 3	21 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d,e]	RR 1.004 (1.001–1.008)	36,871 per 100,000	+165 per 100,000 (+40 to +290)
Hospital Admissions—Lag 4	13 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.003 (0.998–1.007)	36,871 per 100,000	+95 per 100,000 (−85 to +275)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; PM, particulate matter; RR, risk ratio.

[a] The evidence on the impact of environmental exposures on human health outcomes typically comes from nonrandomized studies (NRS). The risk of bias assessment already considers the limitations of lack of randomization; therefore, all studies within the bodies of evidence will start at the same "High" initial certainty within GRADE regardless of study design.

[b] Although most of the studies adjusted for major confounders, unmeasured and uncontrolled confounding cannot be ruled out. Outcome measurement was not done with validated classification criteria and uncertain imputation methods for missing values were used in some of the studies.

[c] Unimportant statistical heterogeneity; most point estimates consistently indicate a harmful effect of increasing pollutant. The analysis detected clinically irrelevant differences as statistically significant variability due to large samples and very narrow 95%CI of included studies.

[d] Asthma exacerbations measured as emergency room visits/hospital admissions (for asthma) from administrative data and registries. Details on how asthma exacerbation was measured or accounted were missing. Administrative data and registries may over or underrepresent the outcome of interest.

[e] The 95%CI includes beneficial as well as a harmful effect. Even though the relative risk appears to be very small, at a population level, even a small effect (beneficial or harmful) may have a relevant impact.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1−exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)−RB.*

TABLE 4 Impact of short-term exposure to CO on asthma exacerbations.

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Baseline risk	Risk difference with a 10 mcg/m^3 increase of CO (95% CI)
ED Visits—Lag 0	6 observational studies	⨁◯◯◯ Very low[a,b,c,d,e]	RR 1.008 (0.888–1.146)	36,871 per 100,000	+311 per 100,000 (−4139 to +5365)
ED Visits—Lag 1	8 observational studies	⨁◯◯◯ Very low[a,b,c,d,e]	RR 1.015 (0.904–1.140)	36,871 per 100,000	+559 per 100,000 (−3537 to +5160 more)
ED Visits—Lag 2	6 observational studies	⨁◯◯◯ Very low[a,b,c,d,e]	RR 0.982 (0.794–1.216)	36,871 per 100,000	−648 per 100,000 (−7613 to +7976)
ED Visits-Lag 3	5 observational studies	⨁◯◯◯ Very low[a,b,c,d,e]	RR 0.990 (0. –1.250)	36,871 per 100,000	+369 per 100,000 (−7959 to +9212)
ED Visits-Lag 4	2 observational studies	⨁◯◯◯ Very low[a,b,c,d,e]	RR 1.045 (0.307–3.556)	36,871 per 100,000	+1645 per 100,000 (−25,558 to +94,260)
Hospital Admissions—Lag 0	10 observational studies	⨁⨁◯◯ Low[a,b,d]	RR 1.012 (0.972–1.054)	36,871 per 100,000	+454 per 100,000 (−1038 to +2009)
Hospital Admissions—Lag 1	11 observational studies	⨁⨁◯◯ Low[a,b,d]	RR 1.011 (0.996–1.026)	36,871 per 100,000	+391 per 100,000 (−165 to +954)
Hospital Admissions-Lag 2	12 observational studies	⨁⨁⨁◯ Moderate[a,b,d]	RR 1.014 (1.008 to 1.021)	36,871 per 100,000	+534 per 100,000 (+307 to +762)
Hospital Admissions—Lag 3	11 observational studies	⨁⨁◯◯ Low[a,b,d]	RR 1.008 (0.998 to 1.019)	36,871 per 100,000	+311 per 100,000 (−71 to +698)
Hospital Admissions—Lag 4	10 observational studies	⨁⨁⨁◯ Moderate[a,b,d]	RR 1.015 (1.006 to 1.025)	36,871 per 100,000	+564 per 100,000 (+207 to +924)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; CO, Carbon monoxide; RR, risk ratio.

[a] The evidence on the impact of environmental exposures on human health outcomes typically comes from nonrandomized studies (NRS). The risk of bias assessment already considers the limitations of lack of randomization; therefore, all studies within the bodies of evidence will start at the same "High" initial certainty within GRADE regardless of study design.

[b]Although most of the studies adjusted for major confounders, unmeasured and uncontrolled confounding cannot be ruled out. Outcome measurement was not done with validated classification criteria and uncertain imputation methods for missing values were used in some of the studies.

[c]Unimportant statistical heterogeneity; most point estimates consistently indicate a harmful effect of increasing pollutant. The analysis detected clinically irrelevant differences as statistically significant variability due to large samples and very narrow 95%CI of included studies.

[d]Asthma exacerbations measured as emergency room visits/hospital admissions (for asthma) from administrative data and registries. Details on how asthma exacerbation was measured or accounted were missing. Administrative data and registries may over or underrepresent the outcome of interest.

[e]The 95%CI includes beneficial as well as a harmful effect. Even though the relative risk appears to be very small, at a population level even a small effect (beneficial or harmful) may have a relevant impact.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1–exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)–RB.*

TABLE 5 Impact of short-term exposure to NO_2 on asthma exacerbations.

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Baseline risk	Risk difference with a 10 mcg/m^3 increase of NO_2 (95% CI)
ED Visits—Lag 0	17 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.003 (0.994–1.012)	36,871 per 100,000	+107 per 100,000 (−234 to +451)
ED Visits—Lag 1	12 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.003 (0.992–1.015)	36,871 per 100,000	+126 per 100,000 (−284 to +541)
ED Visits—Lag 2	9 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.005 (0.988–1.023)	36,871 per 100,000	+196 per 100,000 (−447 to +851)
ED Visits—Lag 3	8 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.010 (1.000–1.020)	36,871 per 100,000	+370 per 100,000 (−5 to +750)
ED Visits—Lag 4	3 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.010 (0.977–1.044)	36,871 per 100,000	+375 per 100,000 (−834 to +1624 more)
Hospital Admissions—Lag 0	35 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 0.997 (0.959–1.037)	36,871 per 100,000	−114 per 100,000 (−1523 to +1352)
Hospital Admissions—Lag 1	26 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.003 (1.000–1.006)	36,871 per 100,000	+106 per 100,000 (+7 to +205)
Hospital Admissions—Lag 2	20 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.005 (1.002–1.008)	36,871 per 100,000	+189 per 100,000 (+89 to +290)
Hospital Admissions—Lag 3	16 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.022 (1.002–1.044)	36,871 per 100,000	+826 per 100,000 (+60 to +1607)
Hospital Admissions—Lag 4	12 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.019 (1.004–1.035)	36,871 per 100,000	+704 per 100,000 (+142 to +1274)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; NO, nitrogen dioxide; R, risk ratio.

[a] The evidence on the impact of environmental exposures on human health outcomes typically comes from nonrandomized studies (NRS). The risk of bias assessment already considers the limitations of lack of randomization; therefore, all studies within the bodies of evidence will start at the same "High" initial certainty within GRADE regardless of study design.

[b] Although most of the studies adjusted for major confounders, unmeasured and uncontrolled confounding cannot be ruled out. Outcome measurement was not done with validated classification criteria and uncertain imputation methods for missing values were used in some of the studies.

[c] Unimportant statistical heterogeneity; most point estimates consistently indicate a harmful effect of increasing pollutant. The analysis detected clinically irrelevant differences as statistically significant variability due to large samples and very narrow 95%CI of included studies.

[d] Asthma exacerbations measured as emergency room visits/hospital admissions (for asthma) from administrative data and registries. Details on how asthma exacerbation was measured or accounted were missing. Administrative data and registries may over or under-represent the outcome of interest.

[e] The 95%CI includes beneficial as well as a harmful effect. Even though the relative risk appears to be very small, at a population level even a small effect (beneficial or harmful) may have a relevant impact.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1−exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)−RB.*

TABLE 6 Impact of short-term exposure to O_3 on asthma exacerbations.

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Baseline risk	Risk difference with a 10 mcg/m^3 increase of O_3 (95% CI)
ED Visits—Lag 0	20 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.005 (0.999–1.011)	36,871 per 100,000	+188 per 100,000 (−32 to +409)
ED Visits—Lag 1	22 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.008 (1.004–1.012)	36,871 per 100,000	+283 per 100,000 (+138 to +429)
ED Visits—Lag 2	10 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.008 (0.998–1.018)	36,871 per 100,000	+295 per 100,000 (−62 to +656)
ED Visits—Lag 3	12 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.012 (0.999–1.025)	36,871 per 100,000	+444 per 100,000 (−39 to +933)
ED Visits—Lag 4	8 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.020 (0.998–1.042)	36,871 per 100,000	+735 per 100,000 (−71 to +1559)
Hospital Admissions—Lag 0	29 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.006 (0.998–1.014)	36,871 per 100,000	+226 per 100,000 (−75 to +529)
Hospital Admissions—Lag 1	24 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.014 (1.007–1.021)	36,871 per 100,000	+510 per 100,000 (+257 to +771)
Hospital Admissions—Lag 2	22 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.011 (1.004–1.019)	36,871 per 100,000	+422 per 100,000 (+130 to +717)
Hospital Admissions—Lag 3	16 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.004 (0.977–1.031)	36,871 per 100,000	+129 per 100,000 (−858 to +1144)
Hospital Admissions—Lag 4	10 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.007 (0.985–1.028)	36,871 per 100,000	+242 per 100,000 (−537 to +1022)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; O_3, ozone; RR, risk ratio.

[a] The evidence on the impact of environmental exposures on human health outcomes typically comes from nonrandomized studies (NRS). The risk of bias assessment already considers the limitations of lack of randomization; therefore, all studies within the bodies of evidence will start at the same "High" initial certainty within GRADE regardless of study design.

[b]Although most of the studies adjusted for major confounders, unmeasured and uncontrolled confounding cannot be ruled out. Outcome measurement was not done with validated classification criteria and uncertain imputation methods for missing values were used in some of the studies.

[c]Unimportant statistical heterogeneity; most point estimates consistently indicate a harmful effect of increasing pollutant. The analysis detected clinically irrelevant differences as statistically significant variability due to large samples and very narrow 95%CI of included studies.

[d]Asthma exacerbations measured as emergency room visits/hospital admissions (for asthma) from administrative data and registries. Details on how asthma exacerbation was measured or accounted were missing. Administrative data and registries may over or under-represent the outcome of interest.

[e]The 95%CI includes beneficial as well as a harmful effect. Even though the relative risk appears to be very small, at a population level even a small effect (beneficial or harmful) may have a relevant impact.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1–exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)–RB.*

TABLE 7 Impact of short-term exposure to SO_2 on asthma exacerbations.

Outcomes	No of studies	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Baseline risk	Risk difference with a 10 mcg/m^3 increase of SO_2 (95% CI)
ED Visits—Lag 0	11 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 0.998 (0.984–1.013)	36,871 per 100,000	−78 per 100,000 (−592 to +477)
ED Visits—Lag 1	9 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.021 (0.981–1.062)	36,871 per 100,000	+756 per 100,000 (−701 to +2272)
ED Visits—Lag 2	7 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.033 (0.970–1.101)	36,871 per 100,000	+1232 per 100,000 (−1110 to +3727)
ED Visits—Lag 3	9 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.030 (0.988–1.075)	36,871 per 100,000	+1112 per 100,000 (−461 to +2752)
ED Visits—Lag 4	2 observational studies	⨁◯◯◯ Very low[a,b,c,d,f]	RR 1.099 (0.360–3.355)	36,871 per 100,000	+3639 per 100,000 (−26,306 to +86,815)
Hospital Admissions—Lag 0	27 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.009 (0.938–1.085)	36,871 per 100,000	+329 per 100,000 (−2276 to +3130)
Hospital Admissions—Lag 1	18 observational studies	⨁⨁⨁◯ Moderate[a,b,c,d]	RR 1.020 (1.005–1.036)	36,871 per 100,000	+740 per 100,000 (+174 to +1315)
Hospital Admissions—Lag 2	21 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.014 (0.983–1.046)	36,871 per 100,000	+509 per 100,000 (−632 to +1685)
Hospital Admissions—Lag 3	15 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.016 (0.985–1.049)	36,871 per 100,000	+601 per 100,000 (−554 to +1793)
Hospital Admissions—Lag 4	10 observational studies	⨁⨁◯◯ Low[a,b,c,d,e]	RR 1.033 (0.996–1.072)	36,871 per 100,000	+1212 per 100,000 (−165 to +2642)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; RR, risk ratio; SO_2, sulfur dioxide.

[a] The evidence on the impact of environmental exposures on human health outcomes typically comes from nonrandomized studies (NRS). The risk of bias assessment already considers the limitations of lack of randomization; therefore, all studies within the bodies of evidence will start at the same "High" initial certainty within GRADE regardless of study design.

[b] Although most of the studies adjusted for major confounders, unmeasured and uncontrolled confounding cannot be ruled out. Outcome measurement was not done with validated classification criteria and uncertain imputation methods for missing values were used in some of the studies.

[c] Unimportant statistical heterogeneity; most point estimates consistently indicate a harmful effect of increasing pollutant. The analysis detected clinically irrelevant differences as statistically significant variability due to large samples and very narrow 95%CI of included studies.

[d] Asthma exacerbations measured as emergency room visits/hospital admissions (for asthma) from administrative data and registries. Details on how asthma exacerbation was measured or accounted were missing. Administrative data and registries may over or underrepresent the outcome of interest.

[e] The 95%CI includes beneficial as well as a harmful effect. Even though the relative risk appears to be very small, at a population level even a small effect (beneficial or harmful) may have a relevant impact.

[f] The 95%CI of effect estimate includes a large beneficial, no effect as well as a large harmful effect which would be translated to a clinically relevant impact.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1–exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)–RB.*

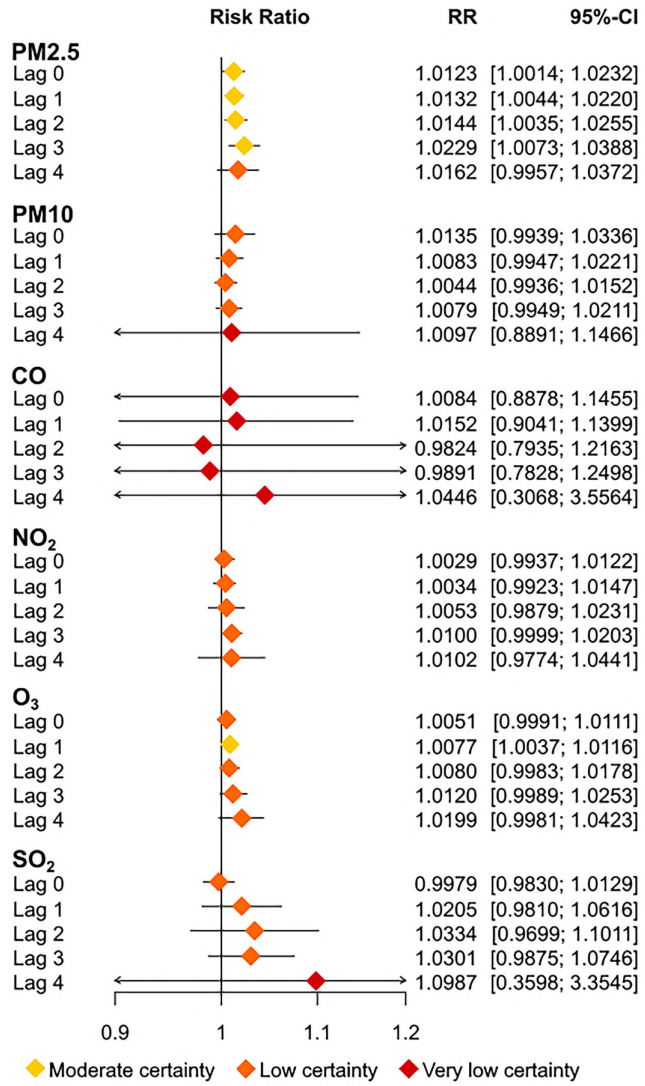

FIGURE 4 Forest plot of meta-analytical values for the association between exposure to pollutant levels and asthma-related emergency department attendance. CO, Carbon monoxide; NO_2, Nitrogen dioxide; O_3, Ozone; PM, Particulate matter; SO_2, Sulfur dioxide.

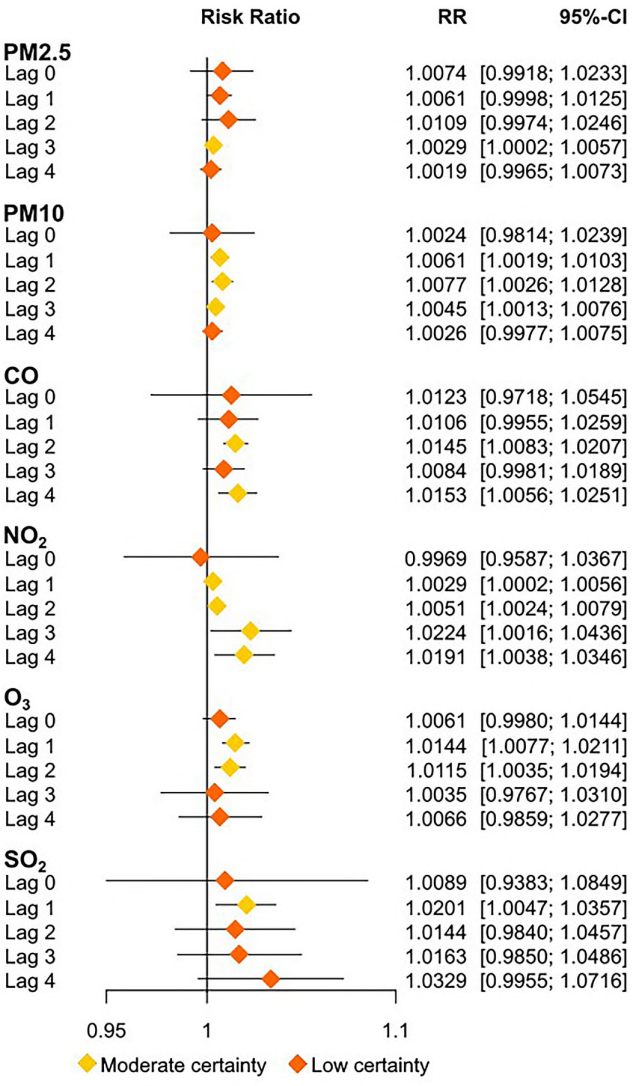

FIGURE 5 Forest plot of meta-analytical values for the association between exposure to pollutant levels and asthma-related hospital admissions. CO, Carbon monoxide; NO_2, Nitrogen dioxide; O_3, Ozone; PM, Particulate matter; SO_2, Sulfur dioxide.

3.2.4 | Quality of life

One study, including adults from 18 to 50 years old, showed that proximity to major roads may negatively affect asthma-related QoL (low certainty). This study reported a negative association between proximity to a roadway and asthma-related QoL (although results were quite imprecise).[52]

3.2.5 | Lung function

Three observational studies assessed the impact of traffic exposure on lung function, reported as FEV1 and PEF % predicted values. The association was found to be unclear and was classified as of very low certainty. Two studies reported an association between better lung function and greater distances from major roadways and lower traffic density in participants both under 18 years[53,60] and over 18 years.[52] However, the estimates obtained were imprecise.

3.2.6 | Asthma symptoms and medication use

Three observational studies reported increased frequency of symptoms (coughing and wheezing) and increased rescue medication use following increased traffic exposure on but the estimates were imprecise for both children[53,61] and the general population,[61] with evidence classified as of very low certainty.

TABLE 8 Exposure to heavy traffic on asthma exacerbations, asthma control, asthma-related QoL, lung function, asthma symptoms, and rescue medication use.

Outcomes	No of studies Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low exposure to traffic*	Risk difference with high exposure to traffic
Hospital Admissions	Two observational studies[17,53] 12 months	⨁⨁◯◯ Low[a,b]	OR 1.4 (0.9–2.2)[17]	630 per 1000	+74 per 1000 (−25 to + 159)
			OR 2.45 (1.23–4.89)[53]	630 per 1000	+177 per 1000 (+47 to + 263)
ED Visits	Three observational studies 1 month[62] 12 months[53] 5 years[55]	⨁◯◯◯ Very low[a,b,c]	OR 1.080 (1.030–1.133)[62,d]	79 per 1000	+6 per 1000 (+2 to + 10)
			OR 1.069 (1.018–1.122)[62,e]	79 per 1000	+5 per 1000 (+1 to + 9)
			OR 1.066 (1.017–1.117)[62,f]	79 per 1000	+5 per 1000 (+1 to + 8)
			OR 1.860 (0.920–1.117)[53]	630 per 1000	+130 per 1000 (−20 to + 250 more)
			OR 1.07 (0.91–1.25)[55,g]	9990 per 10,000	+1 per 10,000 (−1 to + 2)
			OR 1.20 (0.99–1.46)[55,h]	9990 per 10,000	+2 per 10,000 (0 to + 3)
			OR 1.24 (1.00–1.52)[55,i]	9990 per 10,000	2 per 10,000 (0 to + 3)
Asthma exacerbations assessed with a composite end point including hospital admissions, ED visits, and/or repeated outpatient visits	Three observational studies[54,56,59]	⨁⨁◯◯ Low[a,j]	• Lindgren et al[7] reported that for a 10% increase in all traffic exposure measures, there was a 6% to 15% increase in the odds of experiencing an asthma exacerbation. • Chang et al[6] reported that there were higher rates of repeated hospital encounters for children living within 300 m of a major road (relative effect 11%–21% higher), exposed to higher traffic density (relative effect 13%–21% higher), and with 750 or more meters of major road length (relative effect 18% higher) than those without major roads within 300 m of their residences. • Delfino et al[5] reported an increase in repeated hospital encounters, with a relative effect of 7% and 9% increase for an interquartile range increase in traffic-related CO and NO_2, respectively.		
Asthma control assessed with Asthma control questionnaire (ACQ)	One observational study[57]	⨁⨁◯◯ Low[k]	• Epstein et al[8] reported that mean daily high exposures to elemental carbon attributed to traffic were associated with poorer asthma control—an increase in the concentrations from 0.39 to 0.51 μg/m^3 resulted in a 0.5 unit decrease in the ACQ score (clinically meaningful change).		
Asthma-Related Quality of Life assessed with: Marks Asthma QoL. Score 0–60	One observational study[52]	⨁⨁◯◯ Low[l]	• Balmes et al[9] reported a negative association between proximity to a roadway and asthma-related quality-of-life (although results were quite imprecise).		
Lung Function assessed with: FEV1 and PEFR	Three observational studies[52,53,60]	⨁◯◯◯ Very low[a,m]	• Brown et al[2] reported that FEV1 values were not significantly different in children living within 417 m from a major roadway compared to those living at greater distances. • Balmes et[9] reported that FEV1%predicted was positively associated with greater distance from nearest major roadway, meaning better lung function the farther from a roadway. The association was also positive, but imprecise, when measuring distance from nearest road. • Margolis et al[10] reported that FEV1 and PEF %predicted tended to be negatively associated with traffic intensity, meaning worse long function with higher traffic density. Additionally, PEF %predicted was positively associated with longer distances to roads (better lung function with greater distances), but FEV1%predicted was negatively associated.		

TABLE 8 (Continued)

Outcomes	No of studies Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low exposure to traffic*	Risk difference with high exposure to traffic
Asthma symptoms and rescue medication use	Three observational studies[53,58,61]	⨁◯◯◯ Very low[a,n]	• Meng et al[11] reported an increase in the odds of frequent asthma symptoms with increasing traffic density exposure (Relative effect: 50%–92% higher). • Escamilla-Núñez et al[12] reported that with 212 m increase in distance from major roadways, there was a significant decrease in the risk of wheezing. They also reported lower risk of coughing and use of bronchodilator in the same group, but these results were imprecise. • Brown et al[2] reported that children residing within 417 m of a major roadway had increase odds of wheezing that required the use of bronchodilator more than twice a week, than those living further away. Similar result were observed for the odds of daily wheezing.		

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; FEV1, Forced Expiratory Volume at 1 s; PEF, Peak expiratory flow; RR, risk ratio.

[a]Serious concerns about imprecision. There was relevant imprecision on the estimates across studies.

[b]Serious concerns about risk of bias. Brown et al study[2] judged to have a high risk of bias in the measurement of the exposure.

[c]Serious concerns about risk of bias. Sinclair et al study[3] judged to have a moderate risk of bias due to lack of reporting of handling of missing data, and due to lack of controlling for potential confounders.

[d]Exposure: Living within 100 m from a major road.

[e]Exposure: Living 100–200 m from major road.

[f]Exposure: Living 200–300 m from a major road.

[g]Exposure: Traffic density with a 50 m buffer.

[h]Exposure: Traffic density with a 100 m buffer.

[i]Exposure: Traffic density with a 150 m buffer.

[j]Serious concerns about risk of bias. Delfino et al study[5] judged to have moderate risk of bias due to lack of reporting of handling of missing data.

[k]Very serious concerns about imprecision. Only one study with a small sample size provided evidence for this outcome.

[l]Very serious concerns about imprecision: Only one study with a small sample size provided evidence for this outcome and there was relevant imprecision on the effect estimate.

[m]Very serious concerns about risk of bias. Brown et al study[2] judged to have a high risk of bias due to lack of controlling for necessary potential confounders, and bias in the measurement of the exposure.

[n]Very serious concerns about risk of bias: Brown et al study[2] judged to have a high risk of bias in the measurement of the exposure. Meng and Escamilla-Núñez studies[11,12] judged to have a moderate risk of bias in the measurement of the outcome (self-reported).

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

*The absolute risk was obtained as follows, considering a standardization 5 lag-days: using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1−exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)−RB.*

3.3 | Impact of interventions to reduce pollutant emissions on adverse asthma-related outcomes (Q3)

3.3.1 | Characteristics of studies included

The SR included 10 studies assessing the effect of interventions to reduce pollutant emissions in asthma-related outcomes. The studies included were from North America (40%), Europe (30%), and Asia (30%). Three studies reported the effect of the implementation of policies for emission regulation on asthma, namely (i) changes in fuel sulfur content and the makeup of gasoline, as well as a transition from coal to natural gas-generated electricity in the State of New York,[65] (ii) air pollutant emission reduction policies in Seoul,[66] and (iii) the Emission Reduction Plan for Ports and Goods Movement in the State of California.[72] Three studies assessed the impact of transport restriction related to the Olympic games,[64,67,68] three studies reported the effect of COVID-19 lockdown measures on air quality and asthma-related events,[63,69,70] and one study reported the impact of air quality alerts program on asthma-related ED visits.[71] Five studies assessed both adults and children, three studies assessed only children, and two only adults. Table S12 presents a summary of the risk of bias assessment per domain. There were no studies classified as having a low ROB in all assessed domains. There was only one domain for which there was a "high ROB" classification due to confounding.

Table 9 presents the summary of findings. All primary studies assessed severe asthma exacerbations as their outcome measure (either assessed with asthma ED visits or with asthma hospitalizations). The SR did not find studies assessing asthma control, asthma-related QoL, lung function, asthma symptoms, and asthma medication.

3.3.2 | Severe asthma exacerbations: asthma-related ED visits and/or hospital admissions

Five studies assessed the impact of interventions to reduce pollutant emissions on severe asthma exacerbations as defined either by ED visits or hospital admissions. Overall, the impact was found to be unclear, with very low certainty evidence.

One study assessed the effects of a 5-year period (from 2008 to 2013) implementation of regulation policies on emissions and reported that the lowest incidence rates for hospital admissions and ED visits occurred during immediately after the implementation of restrictions (1.11 per 1000 persons-year and 5.56 per 1000 person-year by 2014 and 2016, respectively).[65] Another study assessed the impact of the emission reduction plan for ports and goods movement and reported a lower frequency of asthma ED visits after implementation of the plan in comparison with the control area. Asthma ED visits decreased with 7.8% (95%CI = 3.3%–17.8%) in the first year, with 11.8% (95%CI = 1.1%–21.4%) in the second year, and with 14.8% (95%CI = 4.4%–24.05%) in the third year after the implementation.[72] Of note, during the assessed period, there were greater changes in NO_2 (but not in PM2.5) exposure among beneficiaries living in the policy implementation area compared to the control area.[72]

One study assessed the effect of minimizing road traffic congestion during the Atlanta Olympic Games, and reported a reduction in asthma-related ED visits (adjusted RR = 0.48; 95%CI = 0.44–0.86) and hospital admission (adjusted RR = 0.93; 95%CI = 0.71–1.22).[64]

One study assessed the effect of the implementation of COVID-19 lockdown restrictions in Bologna, Italy, and reported a decrease of 40% in the pediatric asthma-related emergency referrals, compared to the period of 2015 to 2019.[63] Additionally, the authors reported that during the first lockdown period (March–May 2020), the total acute asthma referrals decreased by 85% compared to the same period in the previous 5 years. During the second lockdown period (mid-October–December 2020), there was a reduction of 51% in acute asthma referrals compared with same period in the previous years.[63]

Lastly, one study reported the effect of an air quality index (AQI) alert program in Canada, which had criteria including daily maximum AQI ≥50 and/or PM2.5 ≤ 2.5 mcg and reported a reduction of asthma-related ED visits by 4.73 cases per 1000,000 people per day (95%CI = 0.55–9.38). Program eligibility also led to a reduction of 2.05 (95% CI = 0.07–4.00) daily ED visits for asthma per 1000,000 people per day, corresponding to a relative reduction of 19% (95% = CI 0%–34%).[71]

One study assessed the effect of the implementation of emission reduction policies in Seoul both in adults and in children. Before the implementation of emission reduction policies (2003–2006 period), hospital visits rates had a steep increasing trend (from 20.72 to 26.16 per 100,000 inhabitants). This steep increase was halted by the emission reduction policies as in the 2007–2011 period, the increase was only 26.93–27.91 cases per 100,000.[66] The evidence was classified as being of very low certainty.

A different study assessed the effect of 1-month vehicle restrictions during the 2008 Beijing Olympic Games, and reported it to be associated with a lower risk of outpatient visits for asthma (adjusted RR = 0.50; 95%CI = 0.47–0.55)[68](low certainty).

Three studies assessed the effect of various interventions to reduce pollutants on asthma-related hospital admissions. One study reported the impact of traffic restrictions implemented during the Summer Asian Games and showed a nonsignificant reduction in hospital admissions after 3 weeks of the policy restriction period (adjusted RR = 0.73; 95%CI = 0.49–1.11).[67] One study assessing the effect of COVID-19 lockdown restrictions in Ireland reported an adjusted RR of 0.73 (95%CI = 0.49–1.11) decrease in asthma-related hospital admissions.[69] A different study performed in Greece found a significant reduction of hospital admissions rates during the lockdown period compared to pre-lockdown 2020 or the control period (2019): The incidence rate (IR) of asthma attack admissions in the lockdown period (IR 0.625) was significantly lower when compared to the Pre-lockdown period (IR 2.8; incidence rate ratio [IRR] = 4.48, $p = .004$) as well as the Pre-Control (IR 2; IRR = 3.2, $p = .034$), Control (IR 1.875; IRR = 3, $p = .033$) and Post-Control (IR 4.5; IRR = 7.2, $p < .001$) periods. IR is expressed as admissions per week and the incidence rate ratios (IRR) compared the IR between the lockdown and each of the remaining study periods.

TABLE 9 Impact of measures reducing pollutants levels on asthma exacerbations.

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Narrative
Severe asthma exacerbations assessed with asthma ED and/or and asthma hospitalization	Five observational studies[63–65,71,72]	⨁◯◯◯ Very Low[a,b,c,d]	• For emissions regulation policies, Hopke et al reported that the lowest incidence (number/1000 persons per year) of asthma-related hospital admissions and ED visits occurred in the period after the implementation of restrictions. • Meng et al reported the number of asthma-related ER visits for patients living in good movement corridors reduced 11.8% (95%CI = −21.4% to −1.1%) in the second year after the implementation of restrictions and 14.8% (95%CI = −24.05% to −4.4%) in the third year, comparing those living in control areas. • Friedman et al reported the reduction on asthma-related emergency care together with hospitalizations after minimization of road traffic congestion during the 1996 Atlanta Olympic Games. Comparing asthma-related ED and hospitalizations during the Olympic period versus the baseline period (without any restrictions), adjusted risk ratios were of 0.48 (95%CI = 0.44–0.86) to 0.93 (95%CI = 0.71 to 1.22), respectively. • For COVID-19 lockdown restrictions, Dondi et al reported a 40% decrease of pediatric emergency asthma-related referrals associated with such restrictions in Italy. In addition, the authors reported a decrease in total acute asthma referrals during the first and the second lockdowns. • With the implementation of an air quality alert program, Chen et al reported a 4.73 cases reduction per 1,000,000 people per day (95% CI 0.55–9.38) for alerts effect; and 2.05 cases reduction per 1,000,000 people per day (95% CI 0.07 to 4.00) for program eligibility effect.
Severe asthma exacerbations assessed with hospital visits rates	Two observational studies[66,68]	⨁◯◯◯ Very low[a,b] ⨁⨁◯◯ Low[e,b]	• For emissions regulation policies, Kim et al reported rates of hospital visit in Seoul were increasing until implementation of such policies. Afterward, this increasing trend stopped for all age groups. This effect was observed both in patients of all ages group and in children. • Li et al reported a reduction on outpatient visits for asthma after 1 month of vehicle restrictions during the 2008 Beijing Olympic Games (adjusted RR during the Olympic period compared to the baseline period without any restrictions = 0.50, 95%CI = 0.47–0.55).
Severe asthma exacerbations assessed with asthma hospitalization	Four observational studies[67,68,70,71]	⨁◯◯◯ Very Low[a,d] ⨁◯◯◯ Very Low[b,e] ⨁◯◯◯ Very Low[b,d,e]	• For traffic restriction due to Summer Asian Games, Lee et al reported a nonsignificant reduction in asthma hospitalizations between baseline (including Olympic period) and 3 weeks after the Olympic period (adjusted RR = 0.73, 95%CI = 0.49–1.11). • For COVID-19 lockdown, Quintyne et al reported a nonsignificant reduction in asthma hospitalizations between the baseline (including lockdown period) and 3 weeks after the lockdown (adjusted RR = 0.73, 95%CI = 0.49–1.11) • Sigala et al reported that reduced admissions rates occurred in the lockdown period compared to the pre-lockdown period in 2020 or 2019. • For alert program, Chen et al reported a 0.46 cases reduction per 1,000,000 people per day (95%CI = 1.38–0.34) for alerts effect and a 0.20 cases reduction per 1,000,000 people per day (95%CI = 0.57 fewer to 0.20 more) for program eligibility effect.

Note: GRADE Working Group grades of evidence.

High certainty: there is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; ED, Emergency department; RR, risk ratio.

[a]Downgraded by two levels due to not including potential confounders (periodicity, other pollutants like pollen, and indoor pollutants interaction); also missing data and misclassification bias during ascertainment of events.

[b]Downgraded by one level due to small number of studies.

[c]Downgraded by one level due to composite outcomes (Friedman2001).

[d]The effect may both be harmful or beneficial (Friedman2001, Chen2018, Lee 2007, Chen2018).

[e]Downgraded by one level due to high-risk bias of missing data, moderate risk of bias on the measurement of outcomes, or moderate risk of bias on the selection of reporting bias.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Furthermore, the concentration of six air pollutants positively correlated with weekly hospital admissions in 2020 before lockdown, and significantly decreased during the lockdown.[70] The effect of these interventions was considered unclear (very low certainty).

The study assessing the impact of the AQI alert program in Canada reported a nonsignificant reduction in asthma-related hospital admissions, with an absolute reduction of 0.46 cases per 1000,000 people per day (95%CI = 1.38 fewer to 0.34 more), and a relative reduction of 28% (95%CI = 44% fewer to 55% more). The program eligibility led to a nonsignificant reduction of 0.20 (95%CI = 0.57 fewer to 0.20 more) daily hospital admissions for asthma, with a relative reduction of 25% (95%CI = 0.49% fewer to 0.08% more).[71]

3.4 | Exposure to outdoor pesticides as a risk factor for new-onset asthma (Q4)

3.4.1 | Characteristics of studies included

The SR included 15 studies assessing the impact of outdoor pesticide exposure in the risk of developing asthma. Most studies were performed in North America (33%) and in Latin America (27%). The number of included participants ranged from 127 to 19,704 subjects. Thirteen studies were cross-sectional[73–85] and two were case–control studies.[86,87] Most studies included adults,[74,75,77,81,82,87] four included children,[73,76,84,86] and two considered participants of any age.[80,85] Three studies evaluated the association between prenatal exposure and the occurrence of asthma,[78,79,83] and one study aimed to assess the use of pesticides during pregnancy.[86] Most studies assessed pesticide exposure through questionnaires and interviews, and only two studies included information on concentration of pesticides metabolites in biological samples.[73,81]

Table S13 presents a summary of the ROB assessment per domain for the included studies. There were no studies classified as having a low ROB in all assessed domains. There were no domains for which there was a "high ROB" classification.

The summary of findings is displayed in Tables 10–17. It was not possible to conduct a meta-analysis due to substantial heterogeneity in the exposure assessment, outcomes reported, and the method of analysis used to estimate the effect size.

3.4.2 | New-onset asthma (ever diagnosed by physician)

Eleven observational studies assessed the association between outdoor exposure to pesticides and incidence of asthma in participants of any age. Eight studies suggested a positive

TABLE 10 Impact of exposure to general pesticides on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever diagnosed by physician) in *patients of any age*	(11 observational studies)[73,74,76,77,79–82,84,86,87]	⨁◯◯◯ Very Low[a,b,c,d]	Eight studies reported a positive association between the use of pesticides and asthma incidence, while three studies did not report a significant association. The included studies assessed different frequencies, quantities, and times of exposure for general pesticides use, making it difficult to compare results.
Incidence of self-reported asthma (ever-diagnosed by physician) in children after *prenatal exposure*	(One observational study)[83]	⨁⨁◯◯ Low[b,c]	One study reported that parental (mothers and fathers) occupational use of pesticides both at preconception (OR = 0.46, 95%CI = 0.14 to 1.51) and at post-conception (OR = 0.74, 95%CI = 0.40–1.37) may not be related to asthma in offspring assessed at ages 0–15 years.

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI: confidence interval; OR: odds ratio.

[a]Downgraded by one level because some studies did not include important confounders such as smoking status, allergic status, history of lung problems, working with dust, or other asthma-related chemical products.

[b]Downgraded by one level due to risk of bias arising from measurement of the exposure and outcomes. Data collected might have introduced recall bias and authors did not measure pesticide exposure quantitatively.

[c]Downgraded by one level due to small sample size and wide confidence intervals.

[d]The effect may be both harmful and beneficial.

TABLE 11 Impact of exposure to organophosphates (OP) on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever-diagnosed by physician) in *patients of any age*	(Five observational studies)[75–77,81,87]	⨁◯◯◯ Very Low[a,b,c,d]	One study reported that three out of nine OP compounds were significantly associated with incidence of allergic asthma (*Parathion*: OR = 2.05, 95%CI = 1.21 to 3.46; *Coumaphos*: OR = 2.34, 95%CI = 1.49 to 3.70; and *Diazinon*: OR = 1.57, 95%CI = 1.05 to 2.35).[87] Three studies did not find any significant association[75,76,81] and one found that rates of asthma were inversely associated with exposure to *Chlorpyrifos* and *Terbufos*.[77]

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Downgraded by one level because one study did not include important confounders such as smoking status, allergic status, history of lung problems, working with dust, or other asthma-related chemical products and the variables are very heterogeneous.

[b]Downgraded by one level due to risk of bias arising from measurement of the exposure and outcomes (variable self-reported physician-diagnosed asthma might be unreliable; additionally, individuals with asthma were more likely to report wheeze than those without asthma).

[c]Downgraded by one level due to small sample size and wide confidence intervals.

[d]The effect may be both harmful and beneficial.

association,[73,74,76,79,80,84,86,87] while three studies did not find a significant association.[77,81,82] The studies included assessed different frequencies, quantities and times of exposure to outdoor pesticides, making it difficult to compare results. Thus, the association was graded as very low certainty (Table 10).

Five studies assessed outdoor exposure to OP, with three suggesting that these compounds are not associated with increased asthma incidence,[75,76,81] one suggesting that exposure to *Parathion*, *Coumaphos*, and *Diazinon* are associated with increased incidence of allergic asthma,[87] and another that exposure to *Chlorpyrifos* and *Terbufos* are inversely associated with incident asthma[77] (Table 11). Three studies assessed carbamates—one study reported a positive association between carbamate exposure and self-reported asthma (OR = 1.90; 95%CI = 1.20–3.00),[85] while the remaining two did not find a significant association[75,87] (Table 12). The exposure to fumigants such as 80/20 mix (OR = 2.15; 95%CI = 1.23–3.76) or ethylene dibromide (OR = 2.07; 95%CI = 1.02–4.20) may increase the risk of asthma onset in agricultural workers.[75,85,87] Finally, the associations between (i) exposure to organochlorines,[76,77,81] pyrethroids,[76,81] insecticides,[75,76,83,84,87] or fungicides[76,83,87] (ii) and new-onset asthma were not consistent—each type of pesticide was assessed by a small number of primary studies, with most associations being weak or nonsignificant (Tables 13 and 15–17).

For all associations involving exposure to specific pesticides and incidence of asthma, evidence was considered of very low certainty. The only exception was that of fumigants (low certainty of evidence).

3.4.3 | Prenatal exposure

One study assessed the impact of parental exposure (mother and father) to occupational use of pesticides and reported that both preconception exposure (OR = 0.46; 95%CI = 0.14–1.51) and postconception exposure (OR = 0.74; 95%CI = 0.40–1.37) may not be related to the risk of new-onset asthma in the offspring assessed at ages 0–15 years (low certainty of evidence) (Table 10).[83]

One study reported that the fumigants *metam sodium* (OR = 1.20; 95%CI = 0.80–1.80) and *1,3-dichloropropene* (OR = 1.30; 95%CI = 0.90–2.00) may be associated with asthma incidence in children, although associations were not significant and certainty of the evidence was low[78] (Table 14). Another study concluded that prenatal high pyrethroid metabolite concentrations in urine presented an inverse association with doctor-diagnosed asthma in 5-year old children (pyrethroids: OR = 0.39, 95%CI = 0.13–0.98; 2,4-D: OR = 0.46, 95%CI = 0.16–1.11; and DCCA: OR = 0.21, 95%CI = 0.05–0.62; Table 15) (low certainty).[79] A third study assessing the use of the agricultural fumigant methyl bromide by parents (Table 14) reported that each 10-fold increase of methyl bromide exposure during the prenatal period (applied within 8 km of the residential area) may be associated with a lower FEV1 (regression coefficient = 0.06 L/s; 95%CI = 0.00–0.12)

TABLE 12 Impact of exposure to carbamates on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever-diagnosed by physician) in *patients of any age*	(Three observational studies)[75,85,87]	⨁◯◯◯ Very Low[a,b,c]	One study found that exposure to carbamates was associated to self-reported asthma (OR = 1.90, 95%CI = 1.20–3.00). One study reported that carbaryl and carbofuran may be associated to allergic asthma in agricultural workers (OR = 1.26, 95%CI = 0.85–1.85 and OR = 1.10, 95%CI = 0.75–1.61, respectively). One study reported that exposure to carbamates ≥10 years may be associated with asthma (OR = 1.09, 95%CI = 0.83–1.45).

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Downgraded by one level because two studies did adjust important confounders such as smoking status, allergic status, history of lung problems, working with dust, or other asthma-related chemical products.

[b]Downgraded by one level due to risk of bias arising from measurement of the exposure and outcomes (variable self-reported physician-diagnosed asthma might be unreliable; additionally, individuals with asthma were more likely to report wheeze than those without asthma).

[c]Downgraded by one level due to small sample size and wide confidence intervals.

and with lower forced expiratory flow 25%–75% (regression coefficient = 0.15 L/s; 95%CI = 0.03–0.27) in children up to 7 years of age (low certainty).[78] Additionally, a 10-fold increase in wind-adjusted prenatal chloropicrin use within 8 km was reported to be positively associated with a lower forced expiratory flow 25%–75% (regression coefficient = 0.11; 95%CI = 0.0–0.21) (low certainty).

3.5 | Exposure to outdoor pesticides as a risk factor for adverse asthma-related outcomes (Q5)

3.5.1 | Characteristics of studies included

The SR included four studies assessing the impact of short-term exposure to outdoor pesticides on asthma-related outcomes. All the included studies were conducted in the USA. Two were longitudinal studies (including cohorts and bidirectional-symmetric case cross-over study),[88,90] one was a time-series analysis,[89] and one was a cross-sectional study.[35] Two studies included only children while two studies included participants of all ages. Table S14 shows a summary of ROB assessment. There were no studies classified as having a low ROB in all assessed domains. There were no domains for which there was a "high ROB" classification. Tables 18–21 present the summary of findings for organophosphates, carbamates, pyrethroids, and microbial pesticides.

3.5.2 | Asthma exacerbations

No significant associations were found between exposure to OP pesticides (namely *chlorpyrifos*, *coumaphos*, *diazinon*, *dichlorvos*, *fonofos*, *malathion*, *phorate*, or *terbufos*), carbamates (of the assessed pesticides and asthma exacerbations, with evidence certainty always being considered of very low certainty).[35]

3.5.3 | Severe asthma exacerbations: ED visits

One study reported that a 0.01 ppb increase in the microbial pesticide 1,3-dichloropropene was associated with increased ED visits (OR = 1.14; 95%CI = 1.12–1.15), even after adjustment for PM2.5, NO_2, temperature, and relative humidity[90] (low certainty evidence (Table 21)). Another study reported that the pyrethroids spraying to control mosquito vectors of West Nile virus season in New York was not associated with increased ED visits in the day after spraying (RR = 0.92; 95%CI = 0.80–1.07) (low certainty evidence).[89]

3.5.4 | Lung function

One study performed in children assessed the effect of exposure to OP pesticides on lung function (Table 18), reporting that for each onefold increase of OP pesticides exposure there was an increase

TABLE 13 Impact of exposure to organochlorines (OC) on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever diagnosed by physician) in *patients of any age*	(Two observational studies)[75,87]	⨁◯◯◯ Very low[a,b,c]	One study reported that seven OC compounds (*aldrin*, *chlordane*, *DDT*, *dieldrin*, *heptachlor*, *lindane*, *and toxaphene*) may be associated with allergic asthma. One study concluded that being exposed to OC does not have a significant association with asthma incidence.

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Downgraded by one level because one study did adjust important confounders such as smoking status, allergic status, history of lung problems, working with dust, or other asthma-related chemical products.

[b]Downgraded by one level due to risk of bias arising from measurement of the exposure and outcomes (variable self-reported physician-diagnosed asthma might be unreliable).

[c]The effect may be both harmful and beneficial.

TABLE 14 Impact of exposure to fumigants on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever-diagnosed by physician) in *patients of any age*	(One observational study)[87]	⨁⨁◯◯ Low[a]	One study reported that two fumigants were associated with allergic asthma (*80/20 mix*: OR = 2.15, 95%CI = 1.23–3.76; *ethylene dibromide*: OR = 2.07, 95%CI = 1.02–4.20).
Incidence of self-reported asthma (ever-diagnosed by physician) in children after *prenatal exposure*	(1One observational study)[78]	⨁⨁◯◯ Low[b,c]	One study found that *metam sodium* (OR = 1.20, 95%CI = 0.80–1.80) and *1,3-dichloropropene*, (OR = 1.30, 95%CI = 0.90–2.00) were possibly associated with asthma incidence in children, although differences were not significant.
Lung function	(One observational study)[78]	⨁⨁◯◯ Low[b,c]	One study reported that a 10-fold increase in wind-adjusted prenatal methyl bromide use within 8 km was associated with higher FEV_1 (regression coefficient = 0.06; 95%CI = 0.0–0.12) and FEF_{25-75} (regression coefficient = 0.15; 95%CI = 0.03–0.27). Additionally, a 10-fold increase in wind-adjusted prenatal chloropicrin use within 8 km was positively associated with FEF_{25-75} (regression coefficient = 0.11; 95%CI = 0.0–0.21).

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; FEF25-75, Forced expiratory flow 25%–75%; FEV1, Forced expiratory volume at 1 s; OR, odds ratio.

[a]Downgraded by two levels due to risk of bias arising from measurement of the exposure and outcomes (variables self-reported physician-diagnosed asthma and outcome data might be unreliable); missing data and misclassification bias.

[b]Downgraded by one level due to risk of misclassification bias because authors did not have information on maternal occupation exposure and the geographic location of maternal workplaces during pregnancy.

[c]Downgraded by one level due to small sample size and wide confidence intervals.

TABLE 15 Impact of exposure to pyrethroids on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence(GRADE)	Narrative
Incidence of self-reported asthma (ever-diagnosed by physician) in *patients of any age*	(Three observational studies)[75,76,87]	⨁◯◯◯ Very low[a,b,c,d]	One study found that exposure to pyrethroids may be related to the incidence of allergic asthma—*permethrin (animals)*: OR = 1.51, 95%CI = 0.92—2.45; *permethrin (crops)*: (OR = 1.52, 95%CI = 0.93–2.48). One study reported that being exposed 1 year to pyrethroids may be related to asthma incidence (OR = 1.22, 95%CI = 0.89–1.68). On the other hand, one study concluded that being exposed to pyrethroids may be not associated with the incidence of asthma.
Incidence of self-reported asthma (ever-diagnosed by physician) in children after *parental exposure*	(One observational study)[79]	⨁⨁◯◯ Low[b,c]	One study reported that prenatal high pyrethroid metabolite concentrations (≥percentile 75) presented an inverse association with doctor-diagnosed asthma in childhood during last 12 months (Σpyrethroids: OR = 0.39, 95%CI = 0.13–0.98; 2,4-D: OR = 0.46, 95%CI = 0.16–1.11; DCCA: OR = 0.21, 95%CI = 0.05–0.62).

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Downgraded by one level because one study did not include important confounders such as smoking status, allergic status, history of lung problems, working with dust, or other asthma-related chemical products and the variables are very heterogeneous.

[b]Downgraded by one level due to risk of bias arising from measurement of the exposure and/or outcomes (variable self-reported physician-diagnosed asthma might be unreliable, additionally, individuals with asthma were more likely to report wheeze than those without asthma).

[c]Downgraded by one level due to small sample size and wide confidence intervals.

[d]The effect may be both harmful and beneficial.

in FEV1 (regression coefficient = 0.21, 95%CI = 0.03–0.39). For bromomethane, a decrease in FEV25-75 was observed (regression coefficient = −0.15, 95%CI = −0.29 to −0.00).[56] Overall, the certainty in evidence was classified as "very low."

3.6 | Exposure to extreme temperatures as a risk factor on adverse asthma-related outcomes (Q7)

3.6.1 | Characteristics of included studies

The SR included 16 studies assessing the impact of exposure to extreme temperatures on asthma-related outcomes. Most of the studies were time-series studies,[91,93–102,104] and had been conducted in China (74%), Oceania (11%), Europe (5%), and North America (5%). The number of included patients ranged from 4467 to 1,289,896 individuals.

There was variability on the temperature between the included geographical areas with the mean temperature ranging from −15.5–28.3°C. Ten studies, evaluated exposures to heatwaves while 12 evaluated exposures to cold spells (Table S8).

Table S15 shows a summary of risk of bias assessment. There were no studies classified as having a low risk of bias in all assessed domains. There were two domains for which some studies displayed a "high risk of bias" classification, namely those related to missing data and measurement of the outcome. Tables 22 and 23 present the summary of findings.

3.6.2 | Severe asthma exacerbations: ED admission

Five studies[91,92,95,96,100] assessed the relationship between heatwaves and asthma-related ED admissions (Table 22). In all studies, heatwaves were defined as a mean temperature exceeding the 95th percentile. Only two studies[95,100] reported the minimum number of days of exposure, which ranged from 2 days to 3 weeks. The findings from the meta-analysis indicated that exposure to heatwaves may increase the risk of being admitted to ED due to asthma exacerbations (RR = 1.34; 95%CI = 1.00–1.78). This would result in between 95 and 1462 more ED admissions per 10,000 patients. Evidence was considered of low certainty.

TABLE 16 Impact of exposure to fungicides on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever diagnosed by physician) in *general population*	(Two observational studies)[76,87]	⨁◯◯◯ Very low[a,b,c]	One study reported that being exposed to *captan* was positively associated to asthma (OR = 1.83, 95%CI = 1.15–2.94), but did not find any significant association for other fungicides. One study did not find any significant association between exposure to fungicides and the incidence of asthma symptoms.

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Downgraded by one level due to risk of bias arising from measurement of the exposure and/or outcomes (variable self-reported physician-diagnosed asthma might be unreliable; additionally, individuals with asthma were more likely to report wheeze than those without asthma).

[b]Downgraded by one level due to small sample size and wide confidence intervals.

[c]The effect may be both harmful and beneficial.

TABLE 17 Impact of exposure to insecticides on asthma incidence.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Incidence of self-reported asthma (ever diagnosed by physician) in *general population*	(Two observational studies)[76,84]	⨁◯◯◯ Very low[a,b,c]	One study reported that insecticide use was associated with self-reported asthma (ever diagnosed by any health-care provider) (OR = 2.0, 95%CI = 1.2–3.3). One study did not find any significant association between exposures to insecticides and asthma incidence.

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.

[a]Downgraded by one level because one study did not include important confounders such as smoking status, allergic status, history of lung problems, working with dust, or other asthma-related chemical products and the variables are very heterogeneous.

[b]Downgraded by one level due to risk of bias arising from measurement of the exposure and/or outcomes (variable self-reported physician-diagnosed asthma might be unreliable, additionally, individuals with asthma were more likely to report wheeze than those without asthma).

[c]The effect may be both harmful and beneficial.

Three studies[95,96,100] examined the association between cold spells and asthma-related ED admissions (Table 23). All studies defined cold spells as events with a mean temperature lower than the fifth percentile. Only two studies[95,100] reported the minimum number of days of exposure, which ranged from 2 days to 3 weeks. The meta-analytical results indicated that exposure to cold spells may increase the risk of emergency care (RR = 1.84; 95%CI = 1.01–3.33), although severe heterogeneity was found (I^2 = 80%). This corresponds to between 235 and 3612 more ED admissions per 10,000 individuals. Evidence was considered of low certainty.

TABLE 18 Impact of exposure to OP on asthma-related outcomes.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Asthma-related exacerbations	(One observational study)[35]	⨁◯◯◯ Very low[a,b,c]	One study did not find significant associations between asthma-related exacerbations and *chlorpyrifos* (OR = 1.2, 95%CI = 0.7–1.9), *coumaphos* (OR = 0.6, 95%CI = 0.2–1.5), *diazinon* (OR = 0.7, 95%CI = 0.4–1.3), *dichlorvos* (OR = 0.8, 95%CI = 0.3–2.6), *fonofos* (OR = 0.6, 95%CI = 0.2–1.7), *malathion* (OR = 0.8, 95%CI = 0.4–1.3), *phorate* (OR = 0.5, 95%CI = 0.1–1.7), and *terbufos* (OR = 0.9, 95%CI = 0.5–1.6).
Lung function	(One observational study)[88]	⨁◯◯◯ Very low[a,b]	One study in children showed that for each onefold increase of OP exposure, a higher FEV_1 (regression coefficient = 0.21, 95%CI = 0.03–0.39) was observed. For each onefold increase of bromomethane, a lower FEV_{25-75} (regression coefficient = −0.15, 95%CI = −0.29 to 0.00) was observed.

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; FEV, Forced expiratory volume; OR, odds ratio.

[a]Downgraded by two level due to missing data and risk of bias arising from measurement of the exposure and outcomes. Missing data and risk of bias in selection of participants into the study.

[b]Downgraded by one level due to small sample size and wide confidence intervals.

[c]The effect may be both harmful and beneficial.

These results remained consistent even when examining age subgroups and when including studies with only low or some concerns about the risk of bias.

3.6.3 | Severe asthma exacerbations: hospital admissions

Four studies[93,96,101,105] evaluated the association between heatwaves and asthma-related hospital admissions (Table 22). All studies considered a mean temperature exceeding the 95th percentile to define heatwaves. Only two studies[93,105] reported the number of days of exposure, with a minimum of 2 days. The meta-analytical results indicated that heatwaves may increase the risk of hospital admissions (RR = 1.30; 95%CI = 1.08–1.58), although severe heterogeneity was found (I^2 = 87%). This corresponds to between 84 and 1290 more HA cases per 10,000 individuals. Evidence certainty was considered low.

Five studies[93,94,96,104,106] assessed the association between cold spells and asthma-related HA (Table 23). The definition of cold spells was heterogeneous across studies, but all of them defined the exposure as a mean temperature of less than the fifth percentile. Four studies described the minimum number of days of exposure, considering a minimum of 2 days. The meta-analytical results indicated that cold spells may increase the risk of hospital admissions (RR = 1.35; 95%CI = 1.01–1.81), although severe heterogeneity was found (I^2 = 90%). This corresponds to between 98 and 1505 more HA cases per 10,000 individuals. Evidence certainty was considered low.

These associations remained consistent across different age subgroups and in the studies with the lowest risk of bias.

3.6.4 | Moderate asthma exacerbations

Only one study[103] evaluated the association between cold spells and moderate asthma exacerbations (Table 23). That study defined cold spells based on temperatures ≤2.5 percentile. However, it did not specify the number of days of exposure. The study suggested that cold spells may increase the odds of having an asthma exacerbation (OR = 1.73; 95%CI = 1.13–2.67, corresponding to between 378 to 3139 more exacerbations per 10,000 individuals). Evidence certainty was considered low.

3.6.5 | Asthma mortality

Two studies assessed the association between heatwaves and asthma mortality.[97,102] Both studies evaluated a Chinese population and defined the exposure based on temperatures ≥95th and 99th percentiles. However, neither of the studies reported the minimum number of days of exposure. One study reported that heatwaves may increase the risk of asthma mortality (RR = 1.09; 95%CI = 0.92–1.29, corresponding to 25–387 more deaths due to heatwaves). The other study found that, in the context of a heatwave, for each increase of one degree centigrade, there was a probable excess risk of asthma

TABLE 19 Impact of exposure to carbamates on asthma-related outcomes.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Asthma-related exacerbations	(One observational study)[35]	⨁◯◯◯ Very low[a,b]	One study did not find an association between asthma-related exacerbations and exposure to *carbaryl* (OR = 0.6, 95%CI = 0.4–1.1), *carbofuran* (OR = 0.9, 95%CI = 0.3–2.9), or *aldicarb* (OR = 2.3, 95%CI = 0.9–6.2).
Lung function	(Two observational studies)[88,89]	⨁◯◯◯ Very low[a,b]	One study indicated that exposure to carbamates was not associated with any clinically relevant change in the mean values of FEV_1 (regression coefficient = 0.01, 95%CI (−0.14 to 0.16)), FVC (regression coefficient = 0.02, 95%CI = −0.13 to 0.17), and FEF_{25-75} (regression coefficient = −0.06, 95%CI = −0.14 to 0.16). One study indicated that multiple exposures to *carbamates* were not associated with clinically relevant changes in FEV_1 (regression coefficient = −0.03, 95%CI = −0.21 to 0.15), FVC (regression coefficient = 0.02, 95%CI = −0.13 to 0.17), and FEF_{25-75}, (regression coefficient = 0.10, 95%CI = −0.07 to 0.26).

Note; GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; FEF, Forced expiratory flow; FEV, Forced expiratory volume in 1 s; FV, Forced vital capacity; OR, odds ratio.

[a]Downgraded by two level due to missing data and risk of bias arising from measurement of the exposure and outcomes. Missing data and risk of bias in selection of participants into the study.

[b]Downgraded by one level due to small sample size and wide confidence intervals.

mortality of approximately 4% (95%CI = 3.10%–5.33%). Evidence was considered of low certainty.

Two studies evaluated the association between cold spell and asthma mortality.[97,102] One study[102] defined the cold spell based on temperatures ≤5th percentile but did not report the minimum number of days of exposure. That study indicated that exposure to cold spells may increase the risk of asthma mortality (RR = 1.04; 95%CI = 1.00–1.08, corresponding to between 11 and 172 more HA per 10,000 persons). On the other hand, one other study[97] defined the cold spell based on temperatures ≤1st percentile, but did not report the minimum number of days of exposure. That study reported that, in the context of a cold spell, for each decrease of 1°C, there was a excess risk of asthma mortality of approximately 4% (95%CI = 2.75%–6.08%). Evidence was considered of low certainty.

A short-term exposure to an increase in 10 mcg/m3 of PM2.5 probably results in more ED visits, an increase of PM10, NO_2, O_3, and SO_2 above the WHO thresholds may result in an increase in ED visits, while an increase of PM2.5, PM10, NO_2, O_3, SO_2, and CO may result in an increase in asthma-related hospital admissions. Exposure to TRAP may result in an increase in hospital admissions and poorer asthma control in adults.

Low to very low certainty of evidence shows that an outdoor pollution reducing plan may prevent severe asthma exacerbations (asthma-related ED visits and hospital admissions).

The evidence is very uncertain for the outdoor pesticide's exposure and its association with asthma incidence in the general population. Exposure to fumigants may be associated with increased risk of new-onset asthma in agricultural workers. Prenatal exposure appears not to be related to increased risk of asthma in the offspring when assessed up to 15 years of age.

For the impact on asthma-related outcomes, the evidence is very uncertain for exposure to organophosphates, carbamates, and pyrethroids and increased risk of asthma exacerbations, while exposure to 1,3-dichloropropene may increase the risk of asthma-related ED visits.

Both heatwaves and cold spells may increase the risk of severe asthma exacerbations (ED visits and hospital admissions) and asthma mortality.

4 | DISCUSSION

4.1 | Main findings

This systematic review comprehensively appraised the quality of the evidence provided by 205 studies evaluating the impact of environmental outdoor exposures including pollutants, pesticides, and extreme temperatures on asthma-related outcomes.

TABLE 20 Impact of exposure to pyrethroids on asthma-related outcomes.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Asthma-related exacerbations	(O observational study)[35]	⨁◯◯◯ Very low[a,b]	One study reported that permethrin exposure was possibly inversely associated to asthma exacerbations, although significant associations were not observed (*animals*: OR = 0.8, 95%CI 0.3–2.0, *crops*: OR = 0.7, 95%CI = 0.3–1.5).
Asthma-related Emergency Department (ED) visits	(One observational study)[89]	⨁⨁◯◯ Low	One study reported that the rates of ED asthma visits were not associated with permethrin spraying either 1 day (RR 0.92; 95% CI, 0.80–1.07) or 5 days after the spraying.

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio; RR, risk ratio.

[a]Downgraded by two level due to missing data and risk of bias arising from measurement of the exposure and outcomes. Missing data and risk of bias in selection of participants into the study.

[b]Downgraded by one level due to small sample size and wide confidence intervals.

TABLE 21 Impact of exposure to 1,3-dichloropropene (1,3-D) on asthma-related outcomes.

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Narrative
Asthma-related Emergency Department (ED) visits	(One observational study)[90]	⨁⨁◯◯ Low[a,b]	One study found that a 0.01 ppb increase in 1,3-D was associated with an increase in the odds of having an asthma ED visit (OR = 1.14, 95%CI = 1.12–1.15). A positive association for age was found between 1,3-D and asthma ED visits among patients.

Note: GRADE Working Group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio; ppb, parts per billion.

[a]Downgraded by one level because one study did not include important confounders such as smoking status, sex, gender, etc.

[b]Downgraded by one level due to missing data and risk of bias arising from measurement of the exposure and outcomes.

4.2 | Results in the context of previous evidence

This systematic review updated the results of Zheng et al. evaluating the association of short-term exposure to air pollutants and severe asthma exacerbations (ED visits and hospital admissions). Our results are in alignment with those previously published,[44] and adds results for PM2.5, PM10, and CO. Other systematic reviews assessing the risk of asthma exacerbations with same day exposure and 1 day lag exposure to air pollutants found similar results.[107,108] However, an important difference with the majority of these reviews, is that, beyond assessing the risk of bias, we also conducted an evaluation of the certainty of the evidence using the GRADE approach.

Most reviews assessing exposure to TRAP evaluated the risk of development of childhood asthma.[109,110] A recent systematic review assessed the effect on several health outcomes, including asthma exacerbations and reported similar results. However, since their main focus was asthma onset, they did not conduct a thorough analysis of the studies assessing impact on asthma.[111,112]

Finally, our study showed the impact of different emission reduction plans on asthma exacerbations, potentially informing

TABLE 22 Impact of extreme temperatures (heatwaves) on asthma exacerbations and mortality.

Outcomes	No of studies Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with non-extreme temperature*	Risk difference with heatwave**
Severe asthma exacerbations assessed with ED admission	Four time series[91,95,96,100] 14 days	⨁⨁◯◯ Low[a,b,c]	RR 1.34 (1.00–1.78)	0.04	95 more per 10,000 (from 0 more to 218 more)
				0.92	1462 more per 10,000 (from 0 more to 3354 more)
Severe asthma exacerbations assessed with hospitalization	Four time series[94,101,104,105] 14 days	⨁⨁◯◯ Low[b,c,d]	RR 1.30 (1.08–1.58)	0.04	84 more per 10,000 (from 22 more to 162 more)
				0.92	1290 more per 10,000 (from 344 more to 2494 more)
Asthma mortality	Two time series[97,102] 14 days	⨁⨁◯◯ Low[e,b,c]	RR 1.09 (0.92–1.29)	0.04	25 more per 10,000 (from 22 fewer to 81 more)
				0.92	387 more per 10,000 (from 344 fewer to 1247 more)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]All the studies included did not adjust for the principal confounding factors. It is probable that the measurement of the exposure and outcome in the studies make a differential error that influences the estimation of the association. We downgrade one level of certainty for the global high risk of bias of the included studies.

[b]A heterogeneity was identified in the estimates, but it is explained because of the differences in the days of exposure, the percentiles to define the exposure, and the follow-up between the studies.

[c]We downgrade one level of certainty for imprecision because wide of the confidence interval included non-effect point.

[d]We downgrade one level of certainty for imprecision because wide of the confidence interval included one imprecision point.

[e]All of the studies included did not adjust for the principal confounding factors. Also, most of the studies did not report important information about the measurement of the exposure and outcome that may affected the estimation. We downgrade one level of certainty considering some concerns about the risk of bias of the included studies.

**The range was constructed in base of the less and the high value reported in the studies that investigated the rate of asthma exacerbation in children's or adults (11). ***The absolute risk was obtained as follows, considering a standardization for 14 lag-days: (1) The IR per year was converted according to the lag-days evaluated for each outcome using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1–exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)–RB.*

TABLE 23 Impact of extreme temperatures (cold spell) on asthma exacerbations and mortality.

Outcomes	No of studies Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with non-extreme temperature*	Risk difference with heatwave**
Severe asthma exacerbations assessed with ED admission	Three time series[95,96,100] 14 days	⨁⨁◯◯ Low[a,b,c]	RR 1.84 (1.01–3.33)	0.04	235 more per 10,000 (from 0 more to 218 more)
				0.92	3612 more per 10,000 (from 0 more to 3354 more)
Severe asthma exacerbations assessed with hospitalization	Five time series[93,94,101,104,106] 14 days	⨁⨁◯◯ Low[a,b,c]	RR 1.35 (1.01–1.81)	0.04	98 more per 10,000 (from 22 more to 162 more)
				0.92	1505 more per 10,000 (from 344 more to 2494 more)
Asthma mortality	Two time series[97,102] 14 days	⨁⨁◯◯ Low[a,d]	RR 1.04 (1.00–1.08)	0.04	11 more per 10,000 (from 22 fewer to 81 more)
				0.92	172 more per 10,000 (from 344 fewer to 1247 more)
Moderate asthma exacerbations	One time series[103] 14 days	⨁⨁◯◯ Low[a,c]	OR 1.73 (1.13–2.67)	0.04	378 more per 10,000 (from 36 more to 468 more)
				0.92	3139 more per 10,000 (from 559 more to 7181 more)

Note: GRADE Working Group grades of evidence.

High certainty: There is high confidence that the true effect lies close to that of the estimate of the effect.

Moderate certainty: There is moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.

Very low certainty: There is very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]All the studies included did not adjust for the principal confounding factors. Also, most of the studies did not report important information about the measurement of the exposure and outcome that may affected the estimation. We downgrade one level of certainty considering some concerns about the risk of bias of the included studies.

[b]A heterogeneity was identified in the estimates, but it is explained because the differences in the days of exposure, the percentiles to define the exposure, and the follow-up between the studies.

[c]We downgrade one level of certainty for imprecision because wide of the confidence interval included one imprecision point.

[d]A heterogeneity was identified in the estimates, but it is explained because of the differences in the days of exposure, the percentiles to define the exposure, the follow-up between the studies, and the type of relative measure estimated for the association.

**The range was constructed in base of the less and the high value reported in the studies that investigated the rate of asthma exacerbation in children's or adults (12). **The absolute risk was obtained as follows, considering a standardization for 14 lag-days: (1) The IR per year was converted according to the lag-days evaluated for each outcome using the formula: r = IR per year/t in a year; (2) The probability for time t was estimated using the formula: RB = 1–exp(−r*t); (3) The absolute risk was estimated with the formula: AR = (RB*RR)−RB.*

decision-making on public health measures. However, there is still an urgent need for global measures to reduce exposure to air pollutants to improve asthma-related outcomes in the adult and pediatric population.[5]

Two recent systematic reviews evaluating the association of pesticide exposure with childhood wheeze and asthma, reported similar results than our review.[113,114] Although most studies suggested a positive association, the authors were unable to reach conclusive results due to variations in the study design and exposure measurements.[113,114] Other reviews have assessed the relationship between specific pesticides exposure in subsets of the population (occupational), and only assessed respiratory outcomes.[36,115–117] In contrast, our review of the evidence includes a range of different types of pesticides, assesses individuals regardless of their occupational groups or residence, and specifically looks for asthma outcomes; therefore, providing a more comprehensive assessment.

We identified a recent systematic review[118] that investigated the relationship between asthma-related outcomes and extreme weather conditions, including heatwaves and cold spells, among others. Despite the broad scope, this review reports some estimates of the effects specific to extreme temperatures, and suggests a positive association with asthma exacerbations, specifically, increase in emergency department visits during heatwaves, and hospital admissions during cold spells. It is important to highlight that the number of studies included in their analysis is smaller, compared to our review, resulting in less precise estimations. Additionally, it is important to highlight that the previous SR did not provide clear definitions for cold spells and heatwaves. In contrast, our review took into consideration the lack of consensus and heterogeneity in defining these terms and provided clear definitions of the exposures, improving the applicability of our findings.

4.3 | Limitations and strengths

This SR included only studies published in English. However, we have reviewed references of previous SRs, and when appropriate, the GDG provided additional studies. Due to the vast number of observational studies retrieved, only one reviewer assessed the risk of bias. However, at least one other reviewer cross-checked this assessment as a quality control. For Q5, most of the studies included did not provide the minimum duration criteria for the exposures, so this variable cannot be evaluated in the analysis. Additionally, due to the limited number of studies available per outcome and the heterogeneity in the reported percentiles of mean temperature, we could not assess the impact of different levels of extreme temperatures. In addition, this SR does not explore potentially synergistic interactions of other outdoor pollutants, including allergens, organic compounds, and viruses upon asthma-related outcomes.

There are several strengths of this systematic review. First, we conducted a comprehensive systematic search in three databases. Second, the SR used rigorous methods to assess the certainty of the evidence. Using the GRADE approach, we considered the relevant aspects that could impact the confidence in the results, namely risk of bias, heterogeneity, indirectness, and imprecision of the estimates. Third, we selected and prioritized a priori the critical and important outcomes for the asthma population. Lastly, we present the results in a format (summary of findings tables) that allows easy communication of the key findings to all stakeholders.

4.4 | Implications for practice and research

Our review provides new knowledge on association between outdoor environmental factors and the risk of new-onset asthma and of adverse asthma-related outcomes. We also evaluated the effect of interventions to reduce pollution on asthma-related outcomes.

Although most of the evidence is of moderate or low quality, these results could be of value for different stakeholders, including policymakers and clinicians. For the former, our findings may support public decisions such as fostering pollution reduction plans and reduce exposure of the adult and pediatric populations. For clinicians, the findings can trigger clinical advice to patients with asthma to avoid exposure to outdoor pollutants or extreme temperatures.

While our findings provide some insight into the phenomenon, more high-quality studies are needed to obtain more precise estimates, and further enhance our understanding of the relationship of the different exposures. An improved methodological approach proving causality instead of associations together with an integrated surveillance network for the overall environmental impact on asthma-related outcomes is a key pillar to move this field forward. More can be achieved by validated criteria for selecting the best assay(s) to assess exposure and the biological response for the research question of interest, by easy-to-implement guidelines for sample collection, by shared repositories and biobanks, and by implementing the exposomics, cross-omics approach, and system biomedicine.

AUTHOR CONTRIBUTIONS

Ioana Agache, Carlos Canelo-Aybar, Josefina Salazar, Marek Jutel, and Cezmi A. Akdis drafted the detailed protocols for the systematic reviews, supervised the overall research process, and wrote the article. Ivan Solá conducted the searches. Marta Roque conducted the analysis. David Rigau, L. Yesenia Rodríguez-Tanta, Wendy Nieto-Gutierrez, Yang Song, Yahveth Cantero-Fortiz, and Juan Carlos Vasquez extracted the data. Pablo Alonso-Coello supervised the overall SR process. All the other authors revised and approved the search protocols, revised the data from the systematic reviews and the final article.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. WHO factsheet: Asthma 2017 Available from: https://www.who.int/news-room/fact-sheets/detail/asthma
2. Global Asthma Network. *The Global Asthma Report*. Auckland; 2018.
3. Raulf M, Buters J, Chapman M, et al. Monitoring of occupational and environmental aeroallergens-EAACI position paper. Concerted action of the EAACI IG occupational allergy and Aerobiology & air Pollution. *Allergy*. 2014;69(10):1280-1299.
4. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet*. 2014;383:1581-1592.
5. Annesi-Maesano I, Forastiere F, Balmes J, et al. The clear and persistent impact of air pollution on chronic respiratory diseases: a call for interventions. *Eur Respir J*. 2021;57(3):2002981.
6. D'Amato G, Akdis CA. Global warming, climate change, air pollution and allergies. *Allergy*. 2020;75(9):2158-2160.
7. Agache I, Miller R, Gern JE, et al. Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: a Practall document. *Allergy*. 2019;74(3):449-463.
8. https://www.who.int/publications/i/item/9789240034228. Accessed 03.02.2023
9. Altman MC, Kattan M, O'Connor GT, et al. Associations between outdoor air pollutants and non-viral asthma exacerbations and airway inflammatory responses in children and adolescents living in urban areas in the USA: a retrospective secondary analysis. *Lancet Planet Health*. 2023;7(1):e33-e44.
10. Nassikas NJ, Spangler K, Wellenius GA. Asthma exacerbations attributable to ozone air pollution in New England. *R I Med J (2013)*. 2021;104(9):20-23.
11. Greenberg N, Carel RS, Derazne E, et al. Different effects of long-term exposures to SO_2 and NO_2 air pollutants on asthma severity in young adults. *J Toxicol Environ Health A*. 2016;79(8):342-351.
12. Chauhan AJ, Inskip HM, Linaker CH, et al. Personal exposure to nitrogen dioxide (NO_2) and the severity of virus-induced asthma in children. *Lancet*. 2003;361(9373):1939-1944.
13. Lai VWY, Bowatte G, Knibbs LD, et al. Residential NO_2 exposure is associated with urgent healthcare use in a thunderstorm asthma cohort. *Asia Pac Allergy*. 2018;8(4):e33.
14. Kim Y, Park EH, Ng CFS, et al. Respiratory function declines in children with asthma associated with chemical species of fine particulate matter (PM2.5) in Nagasaki, Japan. *Environ Health*. 2021;20(1):110.
15. Lee S, Ku H, Hyun C, Lee M. Machine learning-based analyses of the effects of various types of air pollutants on hospital visits by asthma patients. *Toxics*. 2022;10(11):644.
16. Bowatte G, Lodge CJ, Knibbs LD, et al. Traffic related air pollution and development and persistence of asthma and low lung function. *Environ Int*. 2018;113:170-176.
17. Newman NC, Ryan PH, Huang B, Beck AF, Sauers HS, Kahn RS. Traffic-related air pollution and asthma hospital readmission in children: a longitudinal cohort study. *J Pediatr*. 2014;164(6):1396-1402.
18. Pfeffer PE, Mudway IS, Grigg J. Air pollution and asthma: mechanisms of harm and considerations for clinical interventions. *Chest*. 2021;159(4):1346-1355.
19. Lakhdar R, Mumby S, Abubakar-Waziri H, Porter A, Adcock IM, Chung KF. Lung toxicity of particulates and gaseous pollutants using ex-vivo airway epithelial cell culture systems. *Environ Pollut*. 2022;305:119323.
20. Seltzer J, Bigby BG, Stulbarg M, et al. O_3-induced change in bronchial reactivity to methacholine and airway inflammation in humans. *J Appl Physiol*. 1986;60:1321-1326.
21. Aris RM, Christian D, Hearne PQ, Kerr K, Finkbeiner WE, Balmes JR. Ozone-induced airway inflammation in human subjects as determined by airway lavage and biopsy. *Am Rev Respir Dis*. 1993;148:1363-1372.
22. Kim J, Kim YC, Ham J, et al. The effect of air pollutants on airway innate immune cells in patients with asthma. *Allergy*. 2020;75(9):2372-2376.
23. Shin JW, Kim J, Ham S, et al. A unique population of neutrophils generated by air pollutant-induced lung damage exacerbates airway inflammation. *J Allergy Clin Immunol*. 2022;149(4):1253-1269.
24. Michaeloudes C, Abubakar-Waziri H, Lakhdar R, et al. Molecular mechanisms of oxidative stress in asthma. *Mol Aspects Med*. 2022;85:101026.
25. D'Amato G, Akdis CA. Desert dust and respiratory diseases: further insights into the epithelial barrier hypothesis. *Allergy*. 2022;77(12):3490-3492.
26. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
27. Sokolowska M, Quesniaux VFJ, Akdis CA, Chung KF, Ryffel B, Togbe D. Acute respiratory barrier disruption by ozone exposure in mice. *Front Immunol*. 2019;10:2169.
28. Rider CF, Carlsten C. Air pollution and DNA methylation: effects of exposure in humans. *Clin Epigenetics*. 2019;11(1):131.
29. Rosenquist NA, Metcalf WJ, Ryu SY, et al. Acute associations between PM2.5 and ozone concentrations and asthma exacerbations among patients with and without allergic comorbidities. *J Expo Sci Environ Epidemiol*. 2020;30(5):795-804.
30. Agache I, Akdis CA. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypes of allergic diseases. *J Clin Invest*. 2019;129(4):1493-1503.
31. Delfino RJ, Staimer N, Tjoa T, et al. Personal and ambient air pollution exposures and lung function decrements in children with asthma. *Environ Health Perspect*. 2008;116:550-558.
32. Fang X, Huang S, Zhu Y, et al. Short-term exposure to ozone and asthma exacerbation in adults: a longitudinal study in China. *Front Public Health*. 2023;10:1070231.
33. Liu Y, Pan J, Zhang H, et al. Short-term exposure to ambient air pollution and asthma mortality. *Am J Respir Crit Care Med*. 2019;200(1):24-32.
34. Hernández AF, Parrón T, Alarcón R. Pesticides and asthma. *Curr Opin Allergy Clin Immunol*. 2011;11(2):90-96.
35. Henneberger PK, Liang X, London SJ, Umbach DM, Sandler DP, Hoppin JA. Exacerbation of symptoms in agricultural pesticide applicators with asthma. *Int Arch Occup Environ Health*. 2014;87(4):423-432.
36. Mamane A, Baldi I, Tessier J-F, Raherison C, Bouvier G. Occupational exposure to pesticides and respiratory health. *Eur Respir Rev*. 2015;24(136):306-319.
37. Lima C, Falcão MAP, Rosa JGS, Disner GR, Lopes-Ferreira M. Pesticides and their impairing effects on epithelial barrier integrity, Dysbiosis, disruption of the AhR signaling pathway and development of immune-mediated inflammatory diseases. *Int J Mol Sci*. 2022;23(20):12402.
38. Proskocil BJ, Bruun DA, Garg JA, et al. The influence of sensitization on mechanisms of organophosphorus pesticide-induced airway hyperreactivity. *Am J Respir Cell Mol Biol*. 2015;53(5):738-747.
39. Sampath V, Shalakhti O, Veidis E, et al. Acute and chronic impacts of heat stress on planetary health. *Allergy*. 2023;78(8):2109-2120.

40. Agache I, Sampath V, Aguilera J, et al. Climate change and global health: a call to more research and more action. *Allergy*. 2022;77(5):1389-1407.
41. D'Amato M, Molino A, Calabrese G, Cecchi L, Annesi-Maesano I, D'Amato G. The impact of cold on the respiratory tract and its consequences to respiratory health. *Clin Transl Allergy*. 2018;8:20.
42. Han A, Deng S, Yu J, Zhang Y, Jalaludin B, Huang C. Asthma triggered by extreme temperatures: from epidemiological evidence to biological plausibility. *Environ Res*. 2023;216(Pt 2):114489.
43. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
44. Zheng XY, Orellano P, Lin HL, Jiang M, Guan WJ. Short-term exposure to ozone, nitrogen dioxide, and sulphur dioxide and emergency department visits and hospital admissions due to asthma: a systematic review and meta-analysis. *Environ Int*. 2021;150:106435.
45. Higgins J, Morgan R, Rooney A, et al. *Risk of bias in non-randomized studies-of exposure (ROBINS-E)*. Launch Version; 2022.
46. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
47. Pace ND, Multani JK. On the reporting of odds ratios and risk ratios. *Nutrients*. 2018;10(10):1512.
48. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
49. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med*. 2001;20(24):3875-3889.
50. Rücker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I(2) in assessing heterogeneity may mislead. *BMC Med Res Methodol*. 2008;8:79.
51. Schünemann H, Brożek J, Guyatt G, Oxman A. Editors*GRADE handbook for grading quality of evidence and strength of recommendations*. The GRADE Working Group; 2013.
52. Balmes JR, Earnest G, Katz PP, et al. Exposure to traffic: lung function and health status in adults with asthma. *J Allergy Clin Immunol*. 2009;123(3):626-631.
53. Brown MS, Sarnat SE, DeMuth KA, et al. Residential proximity to a major roadway is associated with features of asthma control in children. *PloS One*. 2012;7(5):e37044.
54. Chang J, Delfino RJ, Gillen D, Tjoa T, Nickerson B, Cooper D. Repeated respiratory hospital encounters among children with asthma and residential proximity to traffic. *Occup Environ Med*. 2009;66(2):90-98.
55. Cook AG, deVos AJ, Pereira G, Jardine A, Weinstein P. Use of a total traffic count metric to investigate the impact of roadways on asthma severity: a case-control study. *Environ Health*. 2011;10:52.
56. Delfino RJ, Chang J, Wu J, et al. Repeated hospital encounters for asthma in children and exposure to traffic-related air pollution near the home. *Ann Allergy Asthma Immunol*. 2009;102(2):138-144.
57. Epstein TG, Ryan PH, LeMasters GK, et al. Poor asthma control and exposure to traffic pollutants and obesity in older adults. *Ann Allergy Asthma Immunol*. 2012;108(6):423-428.
58. Escamilla-Nuñez MC, Barraza-Villarreal A, Hernandez-Cadena L, et al. Traffic-related air pollution and respiratory symptoms among asthmatic children, resident in Mexico City: the EVA cohort study. *Respir Res*. 2008;9(1):74.
59. Lindgren P, Johnson J, Williams A, Yawn B, Pratt GC. Asthma exacerbations and traffic: examining relationships using link-based traffic metrics and a comprehensive patient database. *Environ Health*. 2016;15(1):102.
60. Margolis HG, Mann JK, Lurmann FW, et al. Altered pulmonary function in children with asthma associated with highway traffic near residence. *Int J Environ Health Res*. 2009;19(2):139-155.
61. Meng YY, Wilhelm M, Rull RP, English P, Nathan S, Ritz B. Are frequent asthma symptoms among low-income individuals related to heavy traffic near homes, vulnerabilities, or both? *Ann Epidemiol*. 2008;18(5):343-350.
62. Sinclair AH, Melly S, Tolsma D, et al. Childhood asthma acute primary care visits, traffic, and traffic-related pollutants. *J Air Waste Manag Assoc*. 2014;64(5):561-567.
63. Dondi A, Betti L, Carbone C, et al. Understanding the environmental factors related to the decrease in pediatric emergency department referrals for acute asthma during the SARS-CoV-2 pandemic. *Pediatr Pulmonol*. 2022;57(1):66-74.
64. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 summer Olympic games in Atlanta on air quality and childhood asthma. *JAMA*. 2001;285(7):897-905.
65. Hopke PK, Croft D, Zhang W, et al. Changes in the acute response of respiratory diseases to PM2.5 in New York State from 2005 to 2016. *Sci Total Environ*. 2019;677:328-339.
66. Kim H, Kim H, Lee JT. Effect of air pollutant emission reduction policies on hospital visits for asthma in Seoul, Korea; quasi-experimental study. *Environ Int*. 2019;132:104954.
67. Lee JT, Son JY, Cho YS. Benefits of mitigated ambient air quality due to transportation control on childhood asthma hospitalization during the 2002 summer Asian games in Busan, Korea. *J Air Waste Manag Assoc*. 2007;57(8):968-973.
68. Li Y, Wang W, Wang J, Zhang X, Lin W, Yang Y. Impact of air pollution control measures and weather conditions on asthma during the 2008 summer Olympic games in Beijing. *Int J Biometeorol*. 2011;55(4):547-554.
69. Quintyne KI, Kelly C, Sheridan A, Kenny P, O'Dwyer M. Impact of COVID-19 lockdown restrictions: ambient NO_2 and asthma hospital admissions. *Ir Med J*. 2021;114(7):413.
70. Sigala I, Giannakas T, Giannakoulis VG, et al. Effect of COVID-19-related lockdown on hospital admissions for asthma and COPD exacerbations: associations with air pollution and patient characteristics. *J Pers Med*. 2021;11(9):867.
71. Chen H, Li Q, Kaufman JS, et al. Effect of air quality alerts on human health: a regression discontinuity analysis in Toronto, Canada. *Lancet Planet Health*. 2018;2(1):e19-e26.
72. Meng YY, Yue D, Molitor J, Chen X, Su JG, Jerrett M. Reductions in NO_2 and emergency room visits associated with California's goods movement policies: a quasi-experimental study. *Environ Res*. 2022;213:113600.
73. Alhanti B, van Wendel de Joode B, Soto Martinez M, et al. Environmental exposures contribute to respiratory and allergic symptoms among women living in the banana growing regions of Costa Rica. *Occup Environ Med*. 2022;79(7):469-476.
74. Baldi I, Robert C, Piantoni F, et al. Agricultural exposure and asthma risk in the AGRICAN French cohort. *Int J Hyg Environ Health*. 2014;217(4–5):435-442.
75. Cherry N, Beach J, Senthilselvan A, Burstyn I. Pesticide use and asthma in Alberta grain farmers. *Int J Environ Res Public Health*. 2018;15(3):526.
76. Faria NMX, Facchini LA, Fassa AG, Tomasi E. Pesticides and respiratory symptoms among farmers. *Revista De Saude Publica*. 2005;39(6):973-981.
77. Fieten KB, Kromhout H, Heederik D, van Wendel de Joode B. Pesticide exposure and respiratory health of indigenous women in Costa Rica. *Am J Epidemiol*. 2009;169(12):1500-1506.
78. Gunier RB, Raanan R, Castorina R, et al. Residential proximity to agricultural fumigant use and respiratory health in 7-year old children. *Environ Res*. 2018;164:93-99.
79. Islam JY, Hoppin J, Mora AM, et al. Respiratory and allergic outcomes among 5-year-old children exposed to pesticides. *Thorax*. 2023;78(1):41-49.

80. Liu S, Wolters PJ, Zhang Y, et al. Association between greenhouse working exposure and bronchial asthma: a pilot, cross-sectional survey of 5,420 greenhouse farmers from northeast China. *J Occup Environ Hyg*. 2019;16(4):286-293.
81. Mwanga HH, Dalvie MA, Singh TS, Channa K, Jeebhay MF. Relationship between pesticide metabolites, cytokine patterns, and asthma-related outcomes in rural women workers. *Int J Environ Res Public Health*. 2016;13(10):957.
82. Ndlovu V, Dalvie MA, Jeebhay MF. Asthma associated with pesticide exposure among women in rural Western cape of South Africa. *Amer J of Indus Med*. 2014;57(12):1331-1343.
83. Pape K, Svanes C, Sejbæk CS, et al. Parental occupational exposure pre- and post-conception and development of asthma in offspring. *Int J Epidemiol*. 2021;49(6):1856-1869.
84. Patel O, Syamlal G, Henneberger PK, Alarcon WA, Mazurek JM. Pesticide use, allergic rhinitis, and asthma among US farm operators. *J Agromedicine*. 2018;23(4):327-335.
85. Senthilselvan A, McDuffie HH, Dosman JA. Association of asthma with use of pesticides. Results of a cross-sectional survey of farmers. *The Am Rev Od Resp Dis*. 1992;146(4):884-887.
86. Hallit S, Raherison C, Waked M, Salameh P. Association between caregiver exposure to toxics during pregnancy and childhood-onset asthma: a case-control study. *Ir J of all, Asth, and Immunol*. 2017;16(6):488-500.
87. Hoppin JA, Umbach DM, London SJ, et al. Pesticide use and adult-onset asthma among male farmers in the agricultural health study. *Eur Respir J*. 2009;34(6):1296-1303.
88. Benka-Coker W, Hoskovec L, Severson R, Balmes J, Wilson A, Magzamen S. The joint effect of ambient air pollution and agricultural pesticide exposures on lung function among children with asthma. *Environ Res*. 2020;190:109903.
89. Karpati AM, Perrin MC, Matte T, Leighton J, Schwartz J, Barr RG. Pesticide spraying for West Nile virus control and emergency department asthma visits in new York City, 2000. *Environ Health Perspect Agosto de*. 2004;112(11):1183-1187.
90. Gharibi H, Entwistle MR, Schweizer D, Tavallali P, Cisneros R. The association between 1,3-dichloropropene and asthma emergency department visits in California, USA from 2005 to 2011: a bidirectional-symmetric case crossover study. *J Asthma*. 2020;57(6):601-609.
91. Bernstein AS, Sun S, Weinberger KR, Spangler KR, Sheffield PE, Wellenius GA. Warm season and emergency department visits to U.S. Children's hospitals. *Environ Health Perspect*. 2022;130(1):17001.
92. Campbell SL, Remenyi TA, Williamson GJ, White CJ, Johnston FH. The value of local heatwave impact assessment: a case-crossover analysis of hospital emergency department presentations in Tasmania, Australia. *Int J Environ Res Public Health*. 2019;16(19):3715.
93. Chen Y, Kong D, Fu J, et al. Increased hospital admissions for asthma from short-term exposure to cold spells in Beijing, China. *Int J Hyg Environ Health*. 2021;238:113839.
94. Chen Y, Kong D, Fu J, et al. Associations between ambient temperature and adult asthma hospitalizations in Beijing, China: a time-stratified case-crossover study. *Respir Res*. 2022;23(1):38.
95. Fang J, Song J, Wu R, et al. Association between ambient temperature and childhood respiratory hospital visits in Beijing, China: a time-series study (2013-2017). *Environ Sci Pollut Res Int*. 2021;28(23):29445-29454.
96. Lam HCY, Hajat S, Chan EYY, Goggins WB 3rd. Different sensitivities to ambient temperature between first-and re-admission childhood asthma cases in Hong Kong-a time series study. *Environ Res*. 2019;170:487-492.
97. Li M, Zhou M, Yang J, Yin P, Wang B, Liu Q. Temperature, temperature extremes, and cause-specific respiratory mortality in China: a multi-city time series analysis. *Air Qual Atmos Health*. 2019;12(5):539-548.
98. Sohail H, Kollanus V, Tiittanen P, Schneider A, Lanki T. Heat, heatwaves and cardiorespiratory hospital admissions in Helsinki, Finland. *Int J Environ Res Public Health*. 2020;17(21):7892.
99. Wang YC, Lin YK. Temperature effects on outpatient visits of respiratory diseases, asthma, and chronic airway obstruction in Taiwan. *Int J Biometeorol*. 2015;59(7):815-825.
100. Xu Z, Huang C, Hu W, Turner LR, Su H, Tong S. Extreme temperatures and emergency department admissions for childhood asthma in Brisbane, Australia. *Occup Environ Med*. 2013;70(10):730-735.
101. Zhang Y, Peng L, Kan H, et al. Effects of meteorological factors on daily hospital admissions for asthma in adults: a time-series analysis. *PloS One*. 2014;9(7):e102475.
102. Zhao Y, Huang Z, Wang S, et al. Morbidity burden of respiratory diseases attributable to ambient temperature: a case study in a subtropical city in China. *Environ Health*. 2019;18(1):89.
103. Zhu Y, Yang T, Huang S, et al. Cold temperature and sudden temperature drop as novel risk factors of asthma exacerbation: a longitudinal study in 18 Chinese cities. *Sci Total Environ*. 2022;814:151959.
104. Lam HC, Li AM, Chan EY, Goggins WB 3rd. The short-term association between asthma hospitalisations, ambient temperature, other meteorological factors and air pollutants in Hong Kong: a time-series study. *Thorax*. 2016;71(12):1097-1109.
105. Wei Q, Zhong L, Gao J, et al. Diurnal temperature range and childhood asthma in Hefei, China: does temperature modify the association? *Sci Total Environ*. 2020;724:138206.
106. Liu X, He Y, Tang C, et al. Association between cold spells and childhood asthma in Hefei, an analysis based on different definitions and characteristics. *Environ Res*. 2021;195:110738.
107. Huang J, Yang X, Fan F, et al. Outdoor air pollution and the risk of asthma exacerbations in single lag0 and lag1 exposure patterns: a systematic review and meta-analysis. *J Asthma*. 2022;59(11):2322-2339.
108. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. *PloS One*. 2017;12(3):e0174050.
109. 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.
110. Han K, Ran Z, Wang X, et al. Traffic-related organic and inorganic air pollution and risk of development of childhood asthma: a meta-analysis. *Environ Res*. 2021;194:110493.
111. Boogaard H, Patton AP, Atkinson RW, et al. Long-term exposure to traffic-related air pollution and selected health outcomes: a systematic review and meta-analysis. *Environ Int*. 2022;164:107262.
112. 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.
113. Rodrigues MB, Carvalho DS, Chong-Silva DC, et al. Association between exposure to pesticides and allergic diseases in children and adolescents: a systematic review with meta-analysis. *J Pediatr (Rio J)*. 2022;98(6):551-564.
114. Gilden RC, Harris RL, Friedmann EJ, et al. Systematic review: Association of Pesticide Exposure and Child Wheeze and asthma. *Curr Pediatr Rev*. 2023;19(2):169-178.
115. Doust E, Ayres JG, Devereux G, et al. Is pesticide exposure a cause of obstructive airways disease? *Eur Respir Rev*. 2014;23(132):180-192.
116. Ratanachina J, De Matteis S, Cullinan P, et al. Pesticide exposure and lung function: a systematic review and meta-analysis. *Occup Med (Lond)*. 2020;70(1):14-23.

117. Tarmure S, Alexescu TG, Orasan O, et al. Influence of pesticides on respiratory pathology - a literature review. *Ann Agric Environ Med*. 2020;27(2):194-200.
118. Makrufardi F, Manullang A, Rusmawatiningtyas D, Chung KF, Lin SC, Chuang HC. Extreme weather and asthma: a systematic review and meta-analysis. *Eur Respir Rev*. 2023;32(168):230019.

SUPPORTING INFORMATION

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