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EAACI GUIDELINE

EAACI guidelines on environmental science for allergy and asthma: The impact of short-term exposure to outdoor air pollutants on asthma-related outcomes and recommendations for mitigation measures

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Abstract

The EAACI Guidelines on the impact of short-term exposure to outdoor pollutants on asthma-related outcomes provide recommendations for prevention, patient care and mitigation in a framework supporting rational decisions for healthcare professionals and patients to individualize and improve asthma management and for policymakers and regulators as an evidence-informed reference to help setting legally binding standards and goals for outdoor air quality at international, national and local levels. The Guideline was developed using the GRADE approach and evaluated outdoor pollutants referenced in the current Air Quality Guideline of the World Health Organization as single or mixed pollutants and outdoor pesticides. Short-term exposure to all pollutants evaluated increases the risk of asthma-related adverse outcomes, especially hospital admissions and emergency department visits (moderate certainty of evidence at specific lag days). There is limited evidence for the impact of traffic-related air pollution and outdoor pesticides exposure as well as for the interventions to reduce emissions. Due

Abbreviations: ACT, asthma control test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma-related Quality of Life Questionnaire; AQD, Air Quality Directive; AQG, Air Quality Guideline; CO, carbon monoxide; COI, conflict of Interest; COPD, chronic obstructive pulmonary disease; COVID 19, Coronavirus disease 2019; EAACI, European Academy of Allergy and Clinical Immunology; EtD, Evidence to decision; EU, European Union; FEV1, Forced expiratory volume in 1 second; GDG, Guideline Development Group; GHG, greenhouse gases; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HCP, healthcare professional; LRTI, lower respiratory tract infection; LMIC, low- and middle-income countries; MP, microplastic; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; PEF, peak expiratory flow; QoL, quality of life; SoF, summary of findings; SO_2, sulphur dioxide; SR, systematic review; TRAP, traffic-related air pollution; UPF, ultrafine particles; US, United States of America; WHO, World Health Organization.

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to the quality of evidence, conditional recommendations were formulated for all pollutants and for the interventions reducing outdoor air pollution. Asthma management counselled by the current EAACI guidelines can improve asthma-related outcomes but global measures for clean air are needed to achieve significant impact.

KEYWORDS
asthma, environmental science, guidelines, outdoor pollution

1 | INTRODUCTION

1.1 | The link between asthma and outdoor air pollution

Asthma is an environmentally driven, chronic respiratory disease. Specific environmental factors linked to asthma inception and/or progression include indoor and outdoor air pollutants, allergens, viral infections, irritants and occupational factors.[1–6]

According to the World Health Organization (WHO), air pollution is one of the greatest environmental risks to health and is especially linked to increased risk of stroke, heart disease, lung cancer, and both chronic and acute respiratory diseases, including asthma. It affects everyone but has a major impact on vulnerable groups: (a) inhabitants of low- and middle-income countries (LMIC), (contributing with 89% to the 4.2 million premature deaths attributed to outdoor air pollution); (b) children, elderly and pregnant women; (c) patients with chronic diseases or disabled; (d) migrants or educationally or economically disadvantaged.[7–9]

1.1.1 | Major air outdoor air pollutants and asthma

The major outdoor air pollutants are carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter (PM) and sulphur dioxide (SO_2). In addition, exposure may occur as associations between pollutants, such as traffic-related air pollution (TRAP).

CO is a gas produced by the incomplete combustion of carbonaceous fuels such as wood, petrol, charcoal, natural gas and kerosene. NO_2 is commonly released from the combustion of fuels in the transportation and industrial sectors. O_3 at ground level is one of the major constituents of photochemical smog, and it is formed through the reaction of gases, including NO_2, in the presence of sunlight. PM is a common proxy indicator for air pollution and is believed to be the major driver of the excess mortality attributed to outdoor pollutants. PM mainly originate from traffic and transportation, industrial activities, power plants, construction sites, waste burning, wildfires, dust and sand storms and earthquakes.[7,10] The major components of PM are sulphates, nitrates, ammonia, sodium chloride, black carbon (BC), mineral dust and water. PM are generally defined by their aerodynamic diameter, with $PM_{2.5}$ and PM_{10} being the most mentioned by the regulatory framework as relevant for human health. Sources of the largest particles mainly consist of pollen, sea spray and wind-blown dust from erosion, agricultural spaces, roadways and mining operations. The finer particles (i.e., PM_1 and $PM_{2.5}$) are generated from primary sources (e.g., combustion of fuels in power generation facilities, industries or vehicles) and secondary sources (e.g., chemical reactions between gases). Despite its smaller diameter, the typical PM1 particle has a larger physical surface area than other fine particulates like $PM_{2.5}$. This makes PM_1 more likely to carry heavy metals, chemicals and volatile organic compounds on its surface and cause even greater harm when inhaled. Unlike $PM_{2.5}$, PM1 is not regulated, and monitoring technology for PM_1 is limited. Ultrafine particles (UFPs) are airborne particulate matter smaller than 0.1 micron in diameter (sometimes called PM 0.1). Some UFPs measure as small as 0.003 microns. Due to their small size, UFPs are considered among the most dangerous particle pollutants, allowing them to be breathed into the lungs and pass into the bloodstream through the lungs. Emission through combustion from natural or human sources is their most common sources. Because of prevalence of UFPs in cities, where global industrialization and population growth have had the most notable impact on air pollution, human activity is believed to be responsible for the largest share of UFPs. SO_2 is produced from the burning of fossil fuels (coal and oil) and the smelting of mineral ores that contain sulphur. TRAP is a complex mixture of gases and particles resulting from the use of motor vehicles emitting a variety of pollutants including NO_2, elemental carbon, UFPs and $PM_{2.5}$. These pollutants can be emitted directly through the vehicle exhaust as tailpipe emissions or from non-exhaust sources such as evaporative emissions of fuel, the resuspension of dust, the wear of brakes and tires and the abrasion of road surfaces. Typically assessed constituents of TRAP consist of elemental carbon, organic carbon, inorganic components (e.g., metals, sulphate and nitrate) and PM-bound organic components (e.g., polycyclic aromatic hydrocarbons). Typical gaseous measurements include nitrogen oxides and ozone; both are oxidants which can damage the lungs and other internal organs. TRAP are one of the largest contributors to poor air quality, and exposure to traffic emissions has been linked to many adverse health effects, including exacerbation of asthma symptoms and low lung function.[7,11,12]

Multiple studies have shown an association between outdoor air pollutants and poor early life lung growth, development of allergic sensitization, acutely impaired lung function, respiratory tract infections and numerous asthma-related outcomes, such as new-onset asthma, asthma exacerbations and deterioration of asthma control, lung function decline, increased use of asthma medication and of

healthcare resources, including visits to emergency department and hospital admissions.[11,13–20] However, epidemiological studies have often yielded inconsistent findings, and not all studies have found significant associations,[21] which may be related to both variations in statistical, measurement and modelling methodologies between studies and differences between countries and/or regions in the concentrations and composition of outdoor air pollution.

The routes through which outdoor air pollutants induce or aggravate asthma include activation of epithelial cells with the release of epithelial-derived cytokines and initiation of an innate immune response, immune dysregulation and inflammation, apoptosis and damage to the epithelial barrier, perturbation of the respiratory tract microbiome, increased oxidative stress, deposition of extracellular matrix proteins and epigenetic changes (Figure 1).[22–29] Air pollutants cause acute bronchospasm, for example, SO_2, O_3 as an irritant and more chronic effects such as oxidative injury to the airways, leading to inflammation and remodelling. In addition, air pollution may interact with airborne allergens enhancing the risk of atopic sensitization and exacerbation of symptoms in sensitized subjects.[30]

Ozone and PM are the pollutants most linked with triggering asthma symptoms. The health risks associated with PMs are of particular public health relevance, since these pollutants are capable of penetrating deep into the lungs and $PM_{2.5}$, PM1 and UFP can enter the bloodstream generating multi-organ systemic effects. $PM_{2.5}$ have been reported to induce autophagy in the bronchial epithelial cells through activation of AMP-activated protein kinase, drive mitophagy through activating PTEN-induced kinase 1/Parkin pathway and induce cell cycle arrest and senescence.[31] Nitrogen dioxide and SO_2 may also trigger asthma symptom at high concentrations.[32]

Epidemiological studies show associations between outdoor pollutants and new-onset asthma in children.[13,19,32–34] Recent data from the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort linked asthma incidence until age 20 years to estimated concentrations of NO_2, PMs and $PM_{2.5}$ absorbance ('soot') at the residential address and showed that exposure to air pollution, especially from motorized traffic, early in life may have long-term consequences for asthma development, as it is associated with an increased risk of developing asthma through childhood and adolescence into early adulthood.[35]

In addition to single air pollutants, exposure to TRAP as a mixture of different pollutants has negative effects on the lung, such as reduced lung function (especially expiratory flows in both children and adults) and asthma exacerbations. TRAP exposure also increases sensitization to outdoor allergens.[36] Long-term exposure to TRAP can cause lung epithelial injury, inflammation, oxidative and metabolic stress.[27,28] The overall risk estimates from a recent meta-analysis showed statistically significant associations for BC, NO_2, $PM_{2.5}$, PM_{10} exposures and risk of asthma development.[37]

The 2020 inquest of a 9-year-old girl (Ella Adoo Kissi-Debrah) with very severe asthma living close to polluted roads in London concluded that illegal levels of air pollution were responsible for the induction, progression and exacerbation of asthma and her eventual death. This was the first-time air pollution appeared on a death certificate as a contributor to death.[38]

1.1.2 | Exposure to outdoor pesticides and asthma

Chronic exposure to pesticides can affect epithelial barriers, such as skin, airways and intestine, causing increased permeability, leaking, dysbiosis and inflammation, with serious implications for metabolism and homeostasis.[39]

Occupational exposure to outdoor pesticides (such as organophosphates and carbamates) has been associated with increased risk of respiratory symptoms especially in the agricultural sector,[40–42] with most of the studies consistently indicating a high contribution of occupational exposure, up to 18% of the total burden of asthma in the exposed populations. In the AGRICAN study, an increased risk of allergic asthma was observed with crop exposure, pesticide use and early life on a farm.[42] The Agricultural Health Study conducted in the United States (US) provided evidence of the association between occupational pesticides exposure and the occurrence of wheezing in the previous year.[43] Occupational outdoor exposure to insecticides was associated with greater asthma mortality rates and increased prevalence of atopic disease.[44]

A study among US citizens linked non-occupational exposure with organophosphates to asthma in adults.[45] Studies conducted among exposed children revealed that children with asthma may be at risk for negative health outcomes and increased hospital admissions due to pesticides exposure, as well as for developing asthma.[46,47]

1.1.3 | Outdoor pollution mitigation measures and asthma

At an individual level, to reduce the impact of outdoor air pollution on asthma-related outcomes it is recommended during high pollution days to avoid outdoor activities, keep windows closed and use air conditioning to filter the air. Important long-term steps to reduce TRAP concentration are use of public transportation, walking or biking instead of driving.[12,48–50] The use of personal monitors and/or warning systems showing local levels of air pollutant levels is advocated, especially for vulnerable populations.[51–54] Additionally, air pollution monitoring apps can be used.[55,56] Personal monitoring can be combined with global positioning satellite and/or accelerometer data to identify specific high-risk microenvironments. Using this approach, personal exposures to BC, $PM_{2.5}$ and other pollutants can be precisely monitored.[55–61]

Despite the importance of $PM_{2.5}$, only 10% of countries have more than three ground-based $PM_{2.5}$ monitors per million people. A geophysical-hybrid combination of satellite retrievals, chemical transport modelling and ground monitor-based calibration can, however, provide quality long-term global and regional estimates of $PM_{2.5}$ concentrations. A geophysical-hybrid approach has been demonstrated to be effective even with sparse ground-based observation, making it well suited for global air-quality applications.[62]

The Air Quality Index (AQI) is a tool for communicating daily air quality using colour-coded categories and provides statements for each category and for air quality in a certain area, which groups of people may be affected, and steps one can take to reduce exposure

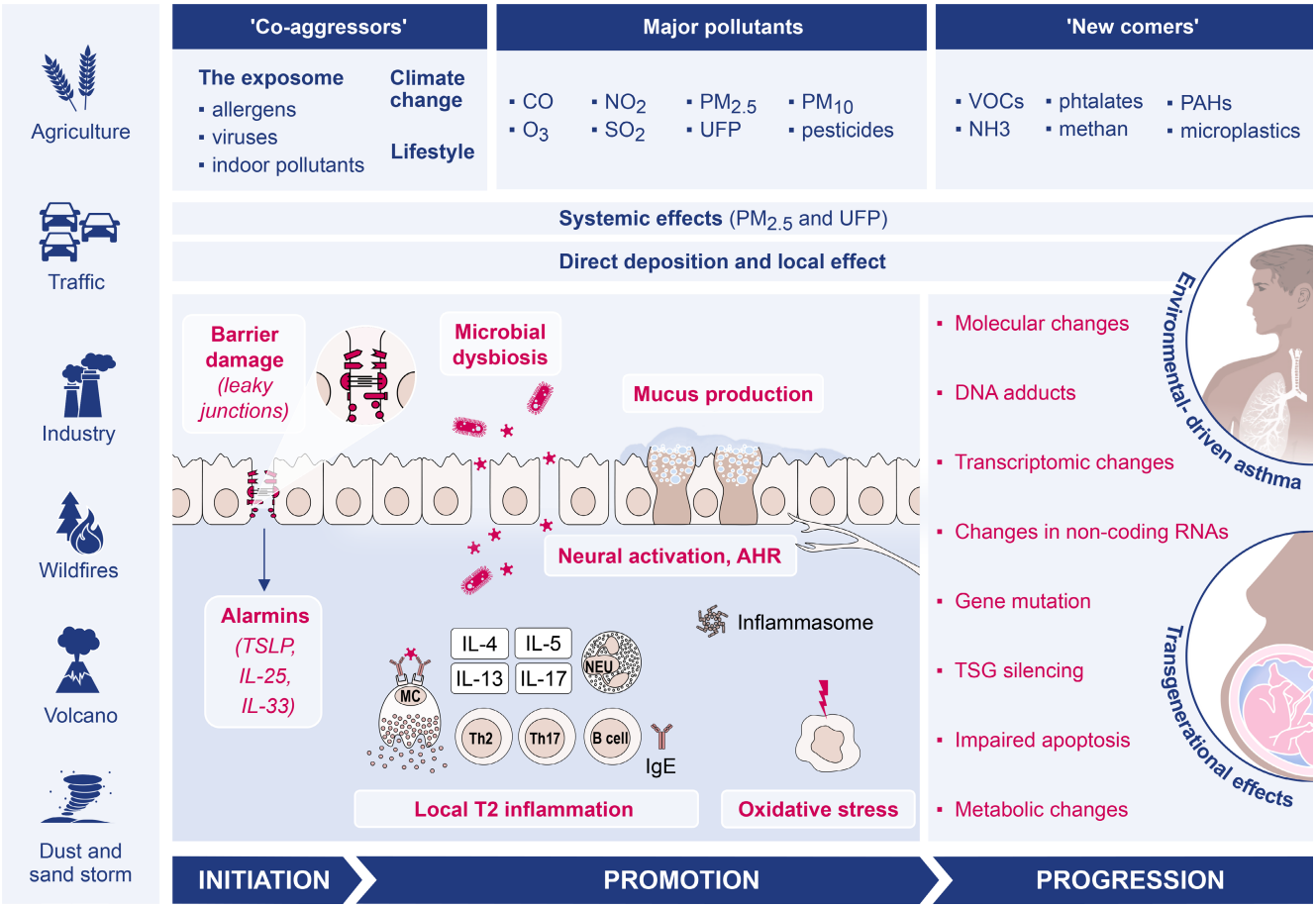

FIGURE 1 The routes through which outdoor air pollutants induce or aggravate asthma. In the complex framework of the exposome, major pollutants and several newly introduced chemicals act in synergy with multiple co-aggressors like allergens, viruses, indoor pollutants, climate change and lifestyle. Outdoor pollutants are generated from a variety of sources, either directly related to human activities (industry, agriculture, traffic) or indirectly amplified by them in the complex frame of climate change (wildfires, dust and sand storms). Natural disasters like volcanic eruptions or earthquakes are also major contributors to outdoor pollution. In the initiation phase, there is barrier damage, activation of epithelial cells with the release of epithelial-derived cytokines and perturbation of the respiratory tract microbiome. In the promotion phase, there is initiation of an innate immune response, immune dysregulation and inflammation, further apoptosis and damage to the epithelial barrier, increased oxidative stress, mucus production, neural activation and amplified airway hyper-reactivity and deposition of extracellular matrix proteins. In the progression phase, molecular, epigenetic changes lead to long-lasting transgenerational effects and environmental-driven asthma endotypes.

to air pollution. It is also used as the basis for air quality forecasts and current air quality reporting.[63,64]

For occupational exposures aside from reducing emissions at source through specific workplace engineering control measures, specific respirators are recommended to prevent the inhalation hazardous chemical agents by workers.[65]

At the societal level, policies that reduce air pollution, such as promoting clean energy and reducing traffic congestion are of paramount importance. The WHO Air Quality Guideline (AQG) and the European Commission Air Quality Directives (AQD) provide recommendations on air quality levels for key air pollutants and qualitative statements on good practices for air pollution management.[66,67] The European AQD are less strict than the WHO AQG. To reduce environmental and health burden due to air pollution, the European Commission has implemented several strategies besides the AQD and is revising the AQD to become more in line with the WHO AQG. The European Green Deal is a response to the burden of air pollution, global warming and climate changes. It aims to protect, conserve and enhance the EU's natural capital, and protect the health and well-being of citizens from environment-related risks and impacts.[68] The main goal is to reduce the emissions of greenhouse gas by 50% by 2030 and to reach climate neutrality by 2050.[69]

The importance of public measures is reflected in a recent report that shows that global population-weighted $PM_{2.5}$ exposure, related to both pollution levels and population size, increased from 1998 (28.3 $\mu g/m^3$) to a peak in 2011 (38.9 $\mu g/m^3$) and decreased steadily afterwards (34.7 $\mu g/m^3$ in 2019). Post-2011 change was related to exposure reduction in China and slowed exposure growth in other regions (especially South Asia, the Middle East and Africa). The post-2011 reduction contributed to a stagnation of growth in global $PM_{2.5}$-attributable mortality.[70]

Although air quality has improved gradually in high-income countries, pollutant concentrations still exceed the 2005 WHO AQGs for several pollutants in many areas. In 2019, more than 90% of the global

population was living in areas where concentrations exceeded the 2005 WHO AQG for long-term exposure to $PM_{2.5}$. Disparities in air pollution exposure are increasing worldwide, particularly as LMIC are experiencing growing levels of air pollution. Air quality has deteriorated in most LMIC, because of large-scale urbanization and economic development that has largely relied on the inefficient combustion of fossil fuels as well as inefficient residential fuel use and industry.[66,67]

1.2 | Purpose of the EAACI guideline

Delivering high-quality clinical care is a central priority for allergists, pneumologists, paediatricians, epidemiologists and other specialities caring for patients with asthma. The European Academy of Allergy and Clinical Immunology (EAACI) develops and updates each year resources to help healthcare professionals (HCPs) and researchers to design the best interventions, deliver high standard care and to assess their actions and decisions for purposes of quality improvement and/or reporting. EAACI Guidelines include recommendations for the management of patients with particular allergic conditions or diseases.

Recognizing asthma as an environmental-driven disease both in its inception and its evolution EAACI developed guidelines on the impact of the outdoor air pollution and on mitigation measures that should be implemented to reduce the burden of outdoor pollution for patients living with asthma.

EAACI Guidelines are developed using the GRADE systematic process and are based on available evidence and the clinical experience and expertise of all interested stakeholders.

1.3 | Target audience

The target audience includes HCPs and scientists involved in the management of asthma, patients and caregivers, regulatory authorities and policymakers. The perspective of the guideline is that of the HCPs.

1.4 | Rationale for the exposures included or excluded

The current guidelines address the effects of short-term exposure to major outdoor pollutants on asthma-related outcomes. Only pollutants listed in the WHO AQG 2021[66] with defined thresholds were included for the systematic reviews (SR) evaluating the impact on asthma-related outcomes. Additionally, the impact of outdoor exposure to pesticides was evaluated. Recommendations are formulated to reflect the benefit for asthma patients from clinical management and policies implemented to reduce the impact of these major pollutants.

The EAACI Guidelines on the impact of short-term exposure to outdoor pollutants on asthma-related outcomes provide a framework for rational decisions for:

a. HCPs and patients to individualize and improve their asthma management
b. for policymakers and regulators as an evidence-informed reference to help setting legally binding standards and goals for outdoor air quality at international, national and local levels.

Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guidelines and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guidelines' recommendations.

2 | METHODS

The EAACI Guidelines followed the GRADE methodology (available at www.gradeworkinggroup.org). Training was conducted with all members of the guidelines development group (GDG) to prepare them for their roles, including specific sessions on the GRADE methodology.

2.1 | The guidelines development group

A Core Leadership Team supervised the project and was responsible together with the Voting Panel for defining the project scope, drafting the clinical questions to be addressed by the guideline, coordinating the literature search and drafting the manuscript (Table S1; in alphabetical order). The GDG was led by three chairs with both content and methodologic expertise. The GDG received support from a methodologist team, who provided advice on the process and provide input on the GRADE summary of findings (SoF) tables and from experts in guideline development.

The methodologist team conducted the SR for each of the clinical questions, graded the quality of evidence, developed the SoF tables and provided the evidence reports. Narrative reviews were conducted by different content specialist subgroups for each topic to be covered to complement the SRs.

The Voting Panel, composed of content experts, decided which clinical questions are to be asked and which outcomes are critical, important and of low importance, and voted for the final recommendations after reviewing the evidence provided by the methodology team and the narrative reviews. It included specialists with expertise and clinical experience in treating asthma, biologists, clinical immunology experts, epidemiologists with a special focus on the exposome, occupational medicine experts, as well as aerobiology, biometeorology and climate change experts.

In accordance with EAACI policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all potential conflict of interest (COIs) in writing at the beginning, middle and end of the project. The Guideline Oversight Committee lead by the EAACI Ethics Committee Chair was responsible for developing and implementing rules related to COIs.

2.2 | Definitions

The population was defined as asthmatic patients, both children and adults.

The guideline focused only on the impact of short-term exposure to outdoor pollutants on asthma-related outcomes. Short-term exposure followed the definition used for the systematic reviews that informed the recommendations and refers to the period of up to 4 days following exposure. We focused on short-term exposure as daily monitoring of air quality is recommended by most environmental agencies as tool to control the immediate impact of air pollution on health outcomes.

The exposure of interest was outdoor air pollution either as (a) single pollutants for separate analysis; (b) mixtures of pollutants presented as TRAP; or (c) outdoor pesticides (organophosphates, carbamates, permethrin, 1,3-dichloropropene). Individual major outdoor pollutants included were CO, NO_2, O_3, $PM_{2.5}$, PM_{10} and SO_2.

The outcomes were defined as asthma-related events (Table 1). Comparisons were made between exposures below or above the WHO thresholds (Questions 1, 2 and 3) or between intervention and no interventions (Question 4).

Day time lags were defined as the time distance between the exposure of interest and the occurrence of the outcomes that were considered.

2.3 | Task force questions and prioritization of outcomes

For this guideline, the following PE(I)CO questions were identified:

(i) Does outdoor air pollution impact asthma-related outcomes?
(ii) Does TRAP exposure impact asthma-related outcomes?
(iii) Does outdoor exposure to pesticides impact asthma-related outcomes?
(iv) Are interventions reducing outdoor air pollution effective in improving asthma-related outcomes?

As a fully developed framework for operationalizing the development of PECO questions does not exist, the CDG followed the recommendations issued by Morgan et al in building the exposure scenarios.[71] As the cut-offs and the size of increments of exposure could be informed iteratively by the WHO thresholds, the scenarios chosen were to evaluate the effect of an exposure cut-off on asthma-related outcomes and to evaluate the potential effect of a cut-off that can be achieved through an intervention to ameliorate the effects of exposure on asthma-related outcomes.

The outcomes evaluated in the SRs were prioritized by the GDG as per GRADE approach as critical or important (Table 1). Critical outcomes include severe asthma exacerbations defined as emergency department visits, hospital admissions and/or systemic use of corticosteroids; asthma control (asthma control questionnaire (ACQ), asthma control test (ACT)) as well as quality of life (QoL). Lung function, asthma symptoms and use of asthma rescue medication were scored as important outcomes.

2.4 | The minimal important difference

The minimal important difference was defined as an increase in exposure to single outdoor pollutants by 10 $\mu g/m^3$.

2.5 | The GRADE approach

Key principles and provisions, key terms, descriptions, PE(I)CO (population, exposure/intervention, comparator and outcomes) questions, search methodology and evidence reporting used in the guideline development process were predefined.

Separate SRs on the impact of exposure to all major outdoor pollutants and outdoor pesticides as well as of regulatory policies to decrease outdoor pollution on asthma-related outcomes were conducted to inform the recommendations.[72] A GRADE SoF table was provided for each PE(I)CO question.

The quality of evidence was evaluated based on GRADE quality assessment criteria by two independent reviewers and discordance resolved by consensus. Quality assessment includes the risk of bias (ROB) of included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced) and imprecision (wide

TABLE 1 Prioritization of the outcomes per GRADE approach.

Outcome	Definition/parameters measured	Importance
Severe asthma exacerbations	Asthma-related ED visits, Asthma-related hospital admission, Systemic corticosteroid use	Critical
Asthma control	Asthma control test (ACT), asthma control questionnaire (ACQ)	Critical
Asthma-related quality of life	AQLQ	Critical
Lung function	FEV1, PEF	Important
Asthma symptoms	Symptom scores	Important
Use of rescue medication		Important

confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval).

The quality of evidence for each outcome was rated as moderate, low or very low. Since only observational studies have been included, high certainty of evidence was not achieved. Search results were pooled in an evidence report as SoF tables and accompanied by a qualitative summary of the evidence for each PE(I)CO question. The Core Leadership Team reviewed the drafted evidence report to address evidence gaps prior to presentation to the Voting Panel.

2.6 | Consensus building and formulating recommendations

After reviewing the evidence report and the additional evidence, the Voting Panel decided in an online plenary meeting followed by subsequent emails regarding the final recommendations. For each PE(I)CO question, the Voting Panel heard an oral summary of the evidence and provided votes on the direction and strength of the related recommendation. A 70% consensus threshold was reached for all recommendation presented below. The recommendations follow the data included in the evidence-to-decision (EtD) tables and take into consideration the balance of desirable and undesirable consequences, quality of evidence, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients and public health impact. A conditional recommendation was provided if there were reasons for uncertainty on the benefit–risk profile, especially for low or very low quality of evidence. The underlying values and preferences played a key role in formulating recommendations. As the key target audience of the EAACI Guidelines is HCPs involved in the management of asthma patients and the patients with asthma themselves the perspective chosen when formulating recommendations was mainly that of HCPs and patients, although the policymakers and the health system perspective were also considered.

Guidance and recommendations are provided per exposure, per outcome and per single lag days. They should be used following the GRADE interpretation (Table 2).

These recommendations will be reconsidered when new evidence becomes available and an update of these guidelines is planned for 2026.

The Guidelines were available on the EAACI website for 2 weeks (29 January 2024-12 February 2024) for public comments. All comments received were carefully revised by the GDG and incorporated where applicable.

2.6.1 | Final review and approval of the guideline by EAACI

In addition to journal and external peer review, the EAACI Executive Committee reviewed the manuscript. This EAACI oversight group did not mandate any of the recommendations to be made within the guideline, but rather served as peer reviewers.

3 | KEY GUIDANCE AND RECOMMENDATIONS

3.1 | PECO 1: Does outdoor air pollution impact asthma-related outcomes? (Exposures in alphabetical order)

3.1.1 | Short-term exposure to CO and asthma-related outcomes

Carbon monoxide (CO) is a dangerous gas that is produced by burning fossil fuels and other organic substances (e.g., wood). When inhaled, CO rapidly binds to haemoglobin in the blood, reducing its ability to carry oxygen. This interferes with oxygen delivery to tissues including the lungs and leads to hypoxemia. Additionally, through modulation of signalling pathways, CO can impact key biological processes including autophagy, mitochondrial biogenesis, programmed cell death (apoptosis), cellular proliferation, inflammation and innate immune responses.[73]

Significant positive exposure-response relationships were found between ambient CO exposure and hospitalization risk for total respiratory diseases, asthma, chronic obstructive pulmonary disease (COPD), lower respiratory tract infection (LRTI) and influenza-pneumonia.

TABLE 2 Interpretation of GRADE recommendations.

Implications	Conditional recommendation
For HCPs	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences
For patients	The majority of individuals in this situation would want the suggested course of action but many would not
For policy makers	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g., shared) decision-making processes can serve as performance measure

TABLE 3 (A) Evidence-to-decision tables supporting guidance for the impact of short-term exposure to CO on asthma-related ED visits (Lags 0–4). (B) Evidence-to-decision tables supporting guidance for the impact of short-term exposure to CO on asthma-related hospitalizations (Lags 2 and 4).

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

Women were more susceptible to ambient CO exposure-associated hospitalizations for asthma and LRTI.[74] Together with ultrafine particles, CO concentrations in the previous 7 days were associated with increases in the relative odds of a paediatric asthma visit.[45,75]

Summary of supportive evidence

Very low certainty of evidence showed that exposure to a 10 μg/m^3 increase of CO is possibly associated with increase in ED visits due to asthma. The point estimates of the relative effects ranged from of 0.982 (Lag 2) to 1.044 (Lag 4).[72]

Moderate quality of evidence showed that exposure to a 10 μg/m^3 increase of CO may be associated with an increase of hospital admissions due to asthma at Lag 2 and Lag 4. The risk ratio was RR 1,014,482 (95% CI 1,008,330 to 1,020,671) and RR 1,015,289 (95% CI 1,005,614 to 1,025,058), respectively. No significant association was detected for Lag 0, Lag 1 or Lag 3; however, the point estimates of the relative effects indicated an increase of hospital admissions ranging from 1008 to 1012 (low certainty of evidence).[72] Full evidence profiles are presented in Table S2.

Recommendations

BOX 1: **Guidance on the impact of short-term CO exposure on asthma-related outcomes**

Short-term exposure to a 10 μg/m^3 increase of CO above the WHO threshold possibly increases the risk of asthma-related emergency department visits (Lags 0–4)	Conditional recommendation
Short-term exposure to a 10 μg/m^3 increase of CO above the WHO threshold increases the risk of asthma-related hospital admissions (Lag 2 and Lag 4)	Conditional recommendation

Justification and additional consideration

Very low certainty evidence showed that exposure to a 10 μg/m^3 increase of CO above the WHO threshold may be related to increased risks of asthma-related emergency department visits. Moderate certainty evidence showed an increased risk of hospital admission at Lag Days 2 and 4. Although the importance of CO on its impact on asthma-related outcomes is widely acknowledged, due to the quality of available evidence the GDG formulated a conditional recommendation, the EtD framework is presented in Table 3.

Subgroups

a. Time to exposure

The risk of hospital admissions due to exposure to CO was increased with moderate certainty of evidence only for Lag Days 2 and 4. Very low to low certainty of evidence showed increased risk of emergency department visits due to asthma following CO exposure at each lag day. Hospital admissions were increased only at Lag Days 0 to 3.[72]

b. Age groups

Children and adults were equally affected.

3.1.2 | Short-term exposure to NO_2 and asthma-related outcomes

Nitrogen dioxide (NO_2) is a gaseous air pollutant produced when fossil fuels such as coal, oil, gas or diesel are burned at high temperatures. NO_2 causes a range of harmful effects on the lungs, including inflammation of the airways, reduced lung function, increased asthma attacks and greater likelihood of asthma-related emergency department visits and/or hospital admissions. Children and the elderly with asthma are generally at greater risk to the negative health effects of NO_2.[76]

Summary of supportive evidence

Low certainty of evidence showed that exposure to a 10 μg/m^3 increase of NO_2 is possibly associated with increases in asthma-related emergency department visits. The point estimates of the relative effects ranged from of 1002 (Lag 0) to 1010 (Lag 4).[72]

Moderate certainty of evidence showed that exposure to a 10 μg/m^3 increase of NO_2 may be associated with an increase of hospital admissions due to asthma at Lag 1, Lag 2, Lag 3 and Lag 4. The risk ratios were RR 1,002,876 (95% CI 1,000,203 to 1,005,557), RR 1,005,130 (95% CI 1,002,411 to 1,007,858), RR 1,022,398 (95% CI 1,001,630 to 1,043,596) and RR 1,019,095 (95% CI 1,003,863 to 1,034,560), respectively.[72] No association was detected for Lag 0, and the point estimate of the relative effect was 0.996 (low certainty of evidence). The full evidence profile is presented in Table S3.

Recommendations

BOX 2: **Guidance on the impact of short-term exposure to NO_2 on asthma-related outcomes**

Short-term exposure to a 10 μg/m^3 increase of NO_2 above the WHO threshold may increase the risk of asthma-related emergency department visits (Lags 0–4)	Conditional recommendation
Short-term exposure to a 10 μg/m^3 increase of NO_2 above the WHO threshold increases the risk of asthma-related hospital admissions (Lags 1–4)	Conditional recommendation

Justification

Low certainty evidence showed that exposure to NO_2 above the WHO threshold has an impact on emergency department visits due to asthma. Moderate certainty evidence showed that exposure to NO_2 leads to increased hospital admissions for asthma from Lag Days 1 to 4.[72] Although the importance of NO_2 on its impact on asthma-related outcomes is widely acknowledged, due to the quality of available evidence reviewed the GDG formulated a conditional recommendation, the EtD framework is presented in Table 4.

Subgroups

a. Time to exposure

There is moderate quality of evidence for increased risk of hospital admissions due to exposure to NO_2 only for Lag Days 1–4. Low certainty of evidence showed that the risk of increased ED visits is possibly associated with NO_2 exposure at each lag day. The risk of hospital admissions due to asthma was increased with low certainty of evidence only at Lag Day 0.[72]

b. Age groups

Children and adults were affected similarly. However, as NO_2 is a major component of TRAP, children are more likely to be affected as compared to adults.

3.1.3 | Short-term exposure to O_3 and asthma-related outcomes

Patients with asthma are a large and growing segment of the general population especially susceptible to the effects of O_3 exposure. Children are at greater risk from exposure to O_3 because their lungs are still developing and they are more likely to be active outdoors when O_3 levels are high. Ozone triggers asthma symptoms and increases asthma severity due to epithelial inflammation and damage, upregulation of adhesion molecules, peri-epithelial immune system activation, increased oxidative stress and glucocorticosteroid resistance.[77,78] Patients with asthma exposed to O_3 had a greater influx in polymorphonuclear leukocytes and larger changes in other markers of airway inflammation than individuals without asthma, suggesting a more intense inflammatory response in asthmatics following

TABLE 4 (A) Evidence-to-decision tables supporting guidance for the impact of short-term exposure to NO_2 on asthma-related ED visits (Lags 0–4). (B) Evidence-to-decision tables supporting guidance for the impact of short-term exposure to NO_2 on asthma-related hospital admissions (Lags 1–4).

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

exposure. Ozone exposure also increases the numbers of eosinophils both in the bronchoalveolar lavage and in the upper airways.[78]

Summary of supportive evidence

Moderate certainty of evidence showed that a 10 μg/m^3 increase of O_3 at Lag 1 is associated with an increase of emergency department visits due to asthma. The risk ratio was RR 1,007,670 (95% CI 1,003,734 to 1,011,622). No association was detected for Lag 0, Lag 2, Lag 3 or Lag 4 with point estimates of the relative effects ranging from of 1005 (Lag 0) to 1019 (Lag 4).[72]

Moderate certainty of evidence showed that a 10 μg/m^3 increase of O_3 at Lag 1 and Lag 2 is associated with an increase of hospital admissions due to asthma. The RRs were 1,013,831 (95% CI 1,006,970 to 1,020,914) and 1,011,452 (95% CI 1,003,528 to 1,019,438), respectively. No association was detected for Lag 0, Lag 3 or Lag 4 however, with point estimates of the relative effects indicating an increase of risk for hospital admissions ranging from 1003 to 1006.[72] Full evidence profile is presented in Table S4.

Recommendations

BOX 3: **Guidance on the impact of short-term O_3 exposure on asthma-related outcomes**

Short-term exposure to a 10 μg/m^3 increase of O_3 above the WHO threshold increases the risk of asthma-related emergency department visits (Lag 1)	Conditional recommendation
Short-term exposure to a 10 μg/m^3 increase of O_3 above the WHO threshold increases the risk of asthma-related hospital admissions (Lag 1 and Lag 2)	Conditional recommendation

Justification

Moderate certainty evidence showed that short-term exposure to O_3 above the WHO threshold has an impact on the emergency department visits and hospital admissions at Lag Day 1 and for hospital admissions at Lag 2 as well.[72] Although the importance of O_3 and its impact on asthma-related outcomes is highly acknowledged, due to the moderate quality of available evidence reviewed the GDG formulated a conditional recommendation, the EtD judgement is included in Table 5.

Subgroups

a. Time to exposure

The risk of increased asthma-related ED visits following the exposure to O_3 above the WHO threshold was increased with moderate certainty of evidence only for Lag Day 1. The risk of hospital admissions was increased with moderate certainty of evidence for Lag Days 1 and 2 after being exposed to O_3.[72]

b. Age groups

Children and adults were equally affected.

3.1.4 | Short-term exposure to $PM_{2.5}$ and asthma-related outcomes

$PM_{2.5}$ is an air pollutant with harmful effects on both human health and the environment. Due to their size, $PM_{2.5}$ particles can reach deep into the respiratory tract causing short-term health effects such as eye, nose, throat and lung irritation, coughing, sneezing, runny nose and shortness of breath. Additionally, $PM_{2.5}$ may also cross the air–blood barrier and reach other organs via the bloodstream. Thus, exposure to $PM_{2.5}$ can also affect heart function and increase the risk for heart attack. People with heart or lung diseases, children and older adults are the most likely to be affected by $PM_{2.5}$ exposure.[79,80] $PM_{2.5}$ exposure is also frequently linked with new-onset asthma.[81]

In addition to its impact on human health, $PM_{2.5}$ can adversely affect climate and ecosystems and biodiversity, thus further impacting asthma and lung health through extreme temperatures, extreme weather events such as dust and sand storms or thunderstorms. Different components of PM can have either warming or cooling effects on the climate. For example, BC, a particulate pollutant from combustion, contributes to the warming of the Earth.[82] Through acidification by wet deposition, $PM_{2.5}$ can cause acid rain to impact aquatic ecosystems.[83]

Summary of supportive evidence

Moderate certainty of evidence showed that a 10 μg/m^3 increase of $PM_{2.5}$ at Lag 0, Lag 1, Lag 2 and Lag 3 is associated with an increase in emergency department visits due to asthma. The RRs were 1,012,266 (95% CI 1,001,443 to 1,023,207), 1,013,155 (95% CI 1,004,419 to 1,021,967), 1,013,980 (95% CI 1,003,455 to 1,024,615) and 1,022,941 (95% CI 1,007,320 to 1,038,804), respectively. No association was detected for Lag 4; however, the point estimate of the relative effect indicated an increase of ED visits of 1.016 (low quality of evidence).[72]

Moderate certainty of evidence showed that a 10 μg/m^3 increase of $PM_{2.5}$ at Lag 3 is associated with an increase in hospital admissions due to asthma. The risk ratio was 1,002,947 (95% CI 1,000,230 to 1,005,672). No association was detected for Lag 0, Lag 1, Lag 2 or Lag 4; however, the point estimate of the relative effect indicated an increase of hospital admissions ranging from of 1001 to 1007 (low quality of evidence).[72] Full evidence profiles are presented in Table S5.

TABLE 5 (A) Evidence-to-decision table supporting guidance for the impact of short-term exposure to O_3 on asthma-related ED visits (Lag 1). (B) Evidence-to-decision table supporting guidance on the impact of short-term exposure to O_3 on asthma-related hospital admissions (Lags 1 and 2).

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

TABLE 6 (A) Evidence-to-decision table supporting guidance on the impact of short-term exposure to $PM_{2.5}$ on asthma-related ED visits (Lags 0–3). (B) Evidence-to-decision table supporting guidance on the impact of short-term exposure to $PM_{2.5}$ on asthma-related hospital admissions (Lag 3).

	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

Recommendations

BOX 4: **Guidance on the short-term $PM_{2.5}$ exposure impact on asthma-related outcomes**

Short-term exposure to a 10 µg/m^3 increase of $PM_{2.5}$ above the WHO threshold increases the risk of asthma-related emergency department visits (Lags 0–3)	Conditional recommendation
Short-term exposure to a 10 µg/m^3 increase of $PM_{2.5}$ above the WHO threshold increases the risk of hospital admissions (Lag 3)	Conditional recommendation

Justification

Moderate certainty evidence showed that exposure to $PM_{2.5}$ above the WHO threshold has an impact on both asthma-related emergency department visits at Lag Days 0–3.[72] Low certainty evidence showed an increased risk of emergency department visits for Lag Day 4. Thus, guidance was formulated only for Lags 0–3. Similarly, as moderate quality evidence was found for exposure to $PM_{2.5}$ and hospitalization for asthma only for Lag 3, guidance was restricted to this particular post-exposure interval. Although the importance of PM and its impact on asthma-related outcomes is highly acknowledged, due to the moderate quality of available evidence the GDG formulated a conditional recommendation, the EtD judgement is presented in Table 6.

Subgroups

a. Time to exposure

The risk of increased emergency department visits due to asthma following exposure to $PM_{2.5}$ above the WHO threshold was increased only at Lag Days 1–3 with moderate certainty of evidence. Similarly, exposure to $PM_{2.5}$ increased the risk of hospital admissions with moderate certainty of evidence only at Lag Day 3.

b. Age groups

Children and adults were equally affected. However, since $PM_{2.5}$ is a component of TRAP, children are more likely to be affected when being exposed.

3.1.5 | Short-term exposure to PM_{10} and asthma-related outcomes

Inhaled PM_{10} can generate a full range of respiratory problems. Short-term exposure to PM_{10} has been associated with coughing, wheezing, worsening of asthma and COPD leading to hospitalization and emergency department visits, and with premature death.[84–87] Exposure to high concentrations of PM_{10} can be particularly harmful to children, elderly people and persons with pre-existing medical conditions.

Summary of supportive evidence

Low certainty of evidence showed that exposure to a 10 μg/m^3 increase of PM_{10} above the WHO threshold is possibly associated with increases in emergency department visits. The point estimates of the relative effects indicated an increase of emergency department visits at all time lags considered ranging from of 1004 to 1013.[72]

Moderate certainty of evidence showed that a 10 μg/m^3 increase of PM_{10} above the WHO threshold at Lag 1, Lag 2 and Lag 3 is associated with an increase in hospital admissions due to asthma. The risk ratios were 1,006,108 (95% CI 1,001,891 to 1.010,342), 1,007,683 (95% CI 1,002,601 to 1,012,790) and 1,004,470 (95% CI 1,001,090 to 1,007,862), respectively. No association was detected for Lag 0 or Lag 4; however, the point estimates of the relative effects indicated an increase of hospital admissions of 1.002 (low quality of evidence).[72] Full evidence profiles are presented in Table S6.

Recommendations

BOX 5: **Guidance on the short-term PM_{10} exposure impact on asthma-related outcomes**

Short-term exposure to a 10 μg/m^3 increase of PM_{10} above the WHO threshold may increase the risk of asthma-related emergency department visits (Lags 0–4)	Conditional recommendation
Short-term exposure to a 10 μg/m^3 increase of PM_{10} above the WHO threshold increases the risk of asthma-related hospital admissions (Lags 1–3)	Conditional recommendation

Justification

Low certainty evidence showed that exposure to PM_{10} above the WHO threshold may increase the risk of increased emergency department visits. Moderate certainty evidence showed an increased risk of hospital admissions upon exposure to PM_{10} at Lag Days 1, 2 and 3; thus, guidance was provided only for this particular interval. Although the importance of PM_{10} and its impact on asthma-related outcomes is highly acknowledged, due to the low or moderate quality of available evidence the GDG formulated a conditional recommendation, the EtD framework is presented in Table 7.

Subgroups

a. Time to exposure

For the risk of increased emergency department visits due to asthma after exposure to PM_{10} above the WHO threshold, there was low certainty of evidence for all lag days. For the risk of hospital admissions, there was moderate quality of evidence at Lag Days 1 to 3.

b. Age groups

Children and adults were equally affected. However, since PM_{10} is a component of TRAP, children are more likely to be affected when being exposed to PM_{10}.

3.1.6 | Short-term exposure to SO_2 and asthma-related outcomes

Sulphur dioxide is produced by burning fossil fuels and by the smelting of mineral ores that contain sulphur. The largest sources of SO_2 emissions are from fossil fuel combustion at power plants and other industrial facilities, as well as industrial processes such as extracting metal from ore, natural sources such as volcanoes, and locomotives, ships, and other vehicles and heavy equipment that burn fuel with a high sulphur content.[88] SO_2 can affect both human health and the environment.

Short-term exposures to SO_2 induce coughing and mucus secretion, acting mainly through afferent neurones and reflex bronchoconstriction, upregulation of vanilloid receptors and down-regulation of tight junctions.[89,90] High concentrations of SO_2 can cause inflammation of the respiratory tract, increase the risk of respiratory tract infections and increase all-cause mortality.[90–95]

Summary of supportive evidence

Low certainty of evidence showed that exposure to a 10 μg/m^3 increase of SO_2 above the WHO threshold is possibly associated with increases in asthma-related emergency department visits. The point estimates of the relative effects ranged from of 0,997 (Lag 0) to 1098 (Lag 4).[72]

Moderate certainty of evidence showed that a 10 μg/m^3 increase of SO_2 above the WHO threshold at Lag 1 is associated with an increase in hospital admissions due to asthma. The risk ratio was 1,020,061 (95% CI 1,004,706 to 1,035,652). No association was detected for Lag 0, Lag 2, Lag 3 or Lag 4. However, the point estimates of the relative effects indicated an increase of hospital admissions ranging from 1008 to 1032 (low quality of evidence).[72] Full evidence profiles are presented in Table S7.

TABLE 7 (A) Evidence-to-decision tables supporting guidance on the impact of short-term exposure to PM 10 on asthma-related ED visits (Lags 0–4). (B) Evidence-to-decision tables supporting guidance on the impact of short-term exposure to PM 10 on asthma-related hospital admissions (Lags 0–4).

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

Recommendations

BOX 6: **Guidance on short-term SO_2 exposure impact on asthma-related outcomes**

Short-term exposure to a 10 μg/m^3 increase of SO_2 above the WHO threshold may increase the risk of asthma-related emergency department visits (Lags 0 to 3)	Conditional recommendation
Short-term exposure to a 10 μg/m^3 increase of SO_2 above the WHO threshold increases the risk of asthma-related hospital admissions (Lag 1)	Conditional recommendation

Justification

Low certainty evidence showed that exposure to SO_2 above the WHO threshold has an impact on the increased risk of emergency department visits at Lag Days 0 to 3. There was very low certainty for Lag 4; thus, guidance was restricted to Lags 0 to 3. Moderate certainty evidence showed that SO_2 exposure increases the risk for asthma-related hospital admissions at lag day one, with low quality evidence for the other post-exposure time points considered; thus, the guidance was restricted to Lag 1. Although the importance of SO_2 and its impact on asthma-related outcomes is highly acknowledged, due to the low or moderate quality of the evidence revised the GDG formulated a conditional recommendation, the EtD judgement is presented in Table 8.

Subgroups

a. Time to exposure

The risk of hospital admissions due to asthma upon exposure to SO_2 was increased with moderate certainty of evidence only for Lag Day 1. There was very low to low certainty of evidence for the risk of increased ED visits at Lag Day 4.[72]

b. Age groups

Children and adults were equally affected.

3.2 | PECO 2: Does TRAP exposure impact asthma-related outcomes?

TRAP derives mainly from the emissions of motor vehicles and from fossil fuel combustion. It contributes significantly to the health impact of the outdoor air pollution, especially in urban settings. In patients with asthma short-term exposure to TRAP (CO, $PM_{2.5}$, UFP, BC and NO_2) induced asymptomatic but consistent reductions in the forced expiratory volume in 1 s (FEV1) accompanied by neutrophilic inflammation and airway acidification.[96] Additionally, TRAP exposure has been associated with all-cause mortality, circulatory, ischemic heart disease, respiratory and lung cancer.[12,97]

3.2.1 | Summary of supportive evidence

Low certainty of evidence showed that higher exposure to TRAP may be associated with an increased risk of asthma exacerbations and of asthma-related hospitalizations, as well as with poorer asthma control.[72] Very low certainty of evidence showed that short-term exposure to TRAP possibly increases the risk of asthma-related emergency department visits, worsens the lung function and asthma-related QoL. Additionally, worsening of asthma symptoms including an increased use of asthma medication is possibly linked to increased TRAP exposure[72] (Table S8).

Exposure to TRAP within 5 km of the participants' residence resulted in an increased risk of repeated hospital encounters of 7% and 9% for an interquartile range increase in traffic-related CO and nitrogen oxides, respectively. The association for NO_2 was approximately

TABLE 8 (A) Evidence-to-decision table supporting guidance on the impact of short-term exposure to SO_2 on asthma-related ED visits (Lags 0–3). (B) Evidence-to-decision table supporting guidance on the impact of short-term exposure to SO_2 on asthma-related hospital admissions (Lag 1).

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

half that for nitrogen oxides (4%). The hazard of repeated hospital encounters increased with increasing vehicle meters travelled/day/m^2 suggesting a potential dose response relation. Additionally, there were higher rates of repeated hospital encounters for children living within 300 m of a major road (11%–21% higher) than those living further away.[72]

Children with a high exposure to TRAP, specifically elemental carbon attributed to traffic, had a 40% increase in the odds of readmission, compared to those with low exposure. There were increased odds of having one or more asthma-related emergency department visits per month for those who lived within 100 m of a major road (8% higher), between 100 m and 200 m (7% higher), or between 200 m and 300 m (6% higher), when compared with participants living at distances greater than 300 m from a major roadway. Both lung function (measured as FEV1% and predicted) and QoL were adversely impacted by TRAP exposure, especially if closer to a major road.[72]

3.2.2 | Recommendations

BOX 7: **Guidance on the impact of short-term TRAP exposure and asthma-related outcomes**

Short-term exposure to TRAP may decrease in asthma control and increase the risk of asthma exacerbations and of hospitalizations for asthma	Conditional recommendation
Short-term exposure to TRAP possibly increases asthma medication use or emergency department visits and possibly decreases lung function or the asthma-related QoL	Conditional recommendation

3.2.3 | Justification

There is low certainty evidence showed that exposure to TRAP has an impact on the increased risk of asthma exacerbations, hospitalization or decreased asthma control. Very low certainty evidence showed that TRAP exposure is associated with increase in asthma medication and emergency department visits as well as decreased lung function and QoL.[72] Although the importance of TRAP exposure and its impact on asthma-related outcomes is highly acknowledged, due to the low quality of available evidence the GDG formulated a conditional recommendation, the EtD judgement is presented in Table 9.

3.2.4 | Age subgroups

Children and adults were equally affected. However, children are especially sensitive to TRAP exposure due to their physiology (rapidly developing organs and systems, higher ventilation rates, smaller in height and thereby closer to the concentrated emissions) and behaviour (more time spent outdoors, playing closer to the ground, etc.).[98]

3.3 | PECO 3: Does outdoor exposure to pesticides impact asthma-related outcomes?

Pesticides are toxic chemicals designed to kill pests, and as such they can pose risks to human health. Acute exposure to pesticides can result in short-term adverse health effects such as stinging eyes, rashes, blisters, blindness, nausea, dizziness, diarrhoea and death.

Pesticide aerosols or gases, like other respiratory irritants, can lead to asthma through interaction with functional irritant receptors in the airway and promoting neurogenic inflammation. Cross-talk between airway nerves and inflammatory cells helps to maintain chronic inflammation that eventually damages the

TABLE 9 (A) Evidence-to-decision tables supporting guidance for TRAP impact on asthma exacerbations and hospitalizations for asthma. (B) Evidence-to-decision tables supporting guidance for TRAP impact on asthma medication use, ED visits, lung function and asthma-related QoL.

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

bronchial epithelium. Certain organophosphate insecticides cause airway hyper-reactivity via a common mechanism of disrupting negative feedback control of cholinergic regulation in the lungs and may also reduce lung function. These pesticides may interact synergistically with allergen sensitization rendering individuals more susceptible for developing asthma.[99–102]

A large-scale human biomonitoring survey conducted in Europe between 2014 and 2021 identified at least 46 pesticides and their metabolites in adults and children across five European countries, with at least two pesticides detected in 84% of the samples collected. The ISA study has provided critical insight into health-related effects of pesticides on the respiratory system, nervous system and reproductive system in mothers and infants.[103–106]

3.3.1 | Summary of supportive evidence

Three studies assessed the impact of pesticides on asthma exacerbations, asthma-related ED visits or hospitalization.[106–108] One study assessed only participants under 18 years of age,[107] while the other two included participants of all ages. The exposure indicators used by these studies include 36 pesticides (herbicides glyphosate, paraquat, herbicide butylate, insecticide aldicarb, etc),[106] pyrethroid[107] and 1,3-dichloropropene (1,3-D).[108]

Although many studies reported estimated effects, conducting meta-analysis was not possible due to substantial heterogeneity in the exposure assessment, outcomes reported, and the method of analysis used to estimate the effect size.

The reported outcomes are classified according to the pesticide type and further classified by type of outcome: asthma-related exacerbations and decrease in respiratory function. Overall, the results were uncertain for asthma-related exacerbations and decrease in respiratory function for organophosphates, carbamates and pyrethroids. Only 1,3-D may be associated with an increased risk of asthma-related emergency department visits (Full evidence profiles are presented in Table S9).

3.3.2 | Recommendations

BOX 8: **Recommendations for outdoor pesticides exposure on asthma-related outcomes**

Exposure to outdoor organophosphates is possibly associated with an increased risk of asthma exacerbation	Conditional recommendation
Exposure to outdoor organophosphates is possibly associated with a decrease in lung function	Conditional recommendation
Exposure to carbamates is possibly associated with an increased risk of asthma exacerbations	Conditional recommendation
Exposure to carbamates is possibly associated with a decrease in lung function	Conditional recommendation
Exposure to permethrin is possibly associated with an increased risk of asthma exacerbations	Conditional recommendation
Exposure to 1,3-dichloropropene (1,3-D) may be associated with an increased risk of asthma exacerbations	Conditional recommendation

3.3.3 | Justification

Very low certainty of evidence showed that exposure to organophosphates, carbamates and permethrin exposure has an impact on asthma exacerbation and lung function. Low certainty of evidence showed that exposure to 1,3-dichloropropene resulted in increased risk of asthma exacerbations.[72] Due to the small number of studies

TABLE 10 Evidence-to-decision tables supporting guidance for pesticides exposure impact on asthma. (A) Exposure to outdoor organophosphates is possibly associated with an increased risk of asthma exacerbation or is possibly associated with a decrease in lung function. (B) Exposure to carbamates is possibly associated with an increased risk of asthma exacerbations or is possibly associated with a decrease in lung function. (C) Exposure to permethrin is possibly associated with an increased risk of asthma exacerbations. (D) Exposure to 1,3-dichloropropene (1,3-D) may be associated with an increased risk of asthma exacerbations.

A						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
B						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
C						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included
D						
	Judgement					
Problem (importance)	No	Probably no	Probably yes	Yes	Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High		No studies included

Note: Yellow means response selected by the Panel.

available that address this question, and the inclusion of only observational studies, a conditional recommendation was formulated. However, the impact of pesticide pollution is certainly an important issue and the danger of it is acknowledged by the GDG. The EtD table is presented in Table 10.

3.3.4 | Age subgroups

The risk of asthma exacerbations following exposure to pesticides is more prominent in adults, especially workers in the agricultural sector. The health effects of exposure to outdoor pesticides may appear at once (at higher doses) or after several days, weeks, months or even years.

3.4 | PICO 4: Are interventions reducing outdoor air pollution effective in improving asthma-related outcomes?

Regulation policies implemented to reduce air pollutants below the WHO threshold include reducing the content of sulphur in fuel, transitioning from carbon-containing materials to more renewable sources of energy (e.g., wind or solar power), replacing diesel and gasoline-powered vehicles with electric vehicles in both the public and private sectors, preventing crop burning or forest fires, using less toxic raw materials or fuels as well as developing less-polluting industrial processes by improving their efficiency.[109–111] Additionally, personal interventions such as avoiding air pollution, filtering air and using face masks in areas with high air pollution also might help to reduce asthma exacerbations.[112,113]

Besides long-term interventions exceptional circumstances measures such as traffic restrictions during the Olympic games and/or lockdown during the COVID-19 pandemic were proved to be useful.

3.4.1 | Summary of supportive evidence

Implementation of regulation policies

Two studies reported the effect of emissions regulations policies. Hopke et al reported a study conducted in New York assessing asthma-related outcomes before, during and after the implementation of the emission regulation policy.[114] The lowest hospitalization and ED visit rates occurred in the period after the implementation of restrictions.

Kim et al reported on a comparison between the population of two cities (one with emission reduction policies introduced and one without), including data from 2001 to 2015. There was a

possible beneficial effect of emission reduction policies on hospital visits for asthma.[115]

Transport restrictions due to Olympic games

Three studies assessing the impact of transport restriction related to the Olympic games were included. One study reported the reduction on outpatient visits for asthma after 1 month of vehicle restrictions during the 2008 Beijing Olympic Games. The adjusted RR for asthma visits during the Olympic period compared to the baseline period (without any restrictions) was 0.50 with 95% CI 0.47–0.55.[116] A second study reported the reduction on asthma-related emergency care together with hospitalization after minimizing road traffic congestion during the 1996 Atlanta Olympic Games. The adjusted RR for asthma-related emergency care and hospitalization during the Olympic period compared to the baseline period (without any restrictions) ranged from 0.48, 95% CI 0.44 to 0.86, to 0.93, 95% CI 0.71 to 1.22 across four databases. The study also evaluated the association between the change of pollutants with the asthma acute events after lifting the restrictions. The adjusted RR for asthma events for 50-ppb incremental change in O_3 was from 1.0, 95% CI 0.61–1.58, to 1.4 (1.01–1.94) and for 10 μg/m^3 incremental change in PM_{10} were from 0.8, 95% CI 0.33–1.88, to 1.8, 95% CI 0.68–4.81.[117] The third study specifically reported on the reduction on the asthma hospitalizations between the baseline period (including the Olympic period) and effective period (3 weeks after the Olympic period). The adjusted RR was 0.73, 95% CI 0.49–1.11.[118]

Restrictions due to COVID-19 pandemic

Three studies reporting the impact of lockdown measures on air quality and asthma-related events were evaluated. Dondi et al reported that an overall 40% decrease of paediatric emergency asthma-related referrals in 2020 compared to the years 2015–2019. During lockdown from March to May 2020, the total acute asthma referrals decreased abruptly by 85% compared to the same period in the previous 5 years. During the second lockdown from mid-October to December 2020, a reduction of 51% compared with the peak usually reported in the autumn was observed. Importantly, there was an extraordinary decrease in the proportion of asthma-related ED visits designated as high-priority during the first lockdown and the subsequent weeks.[119] Quintyne et al reported a reduction in levels of ambient NO_2 across Ireland from 2018 to 2020 associated with decreases in asthma hospital admissions.[120] Sigala et al reported reduced admissions rates in the lockdown period compared to the pre-lockdown 2020 ($p < .001$) or the control, 2019-year ($p = .007$) periods. Furthermore, the concentration of air pollutants positively correlated with weekly hospital admissions in 2020 and significantly decreased during the lockdown.[121] Of note, lack of pollutant exposure coincided with lack of exposure to respiratory viruses usually causing asthma exacerbations so a direct beneficial effect cannot be claimed.

3.4.2 | Recommendations

BOX 9: **Guidance on the impact of regulation policies and specific interventions to decrease outdoor pollutants on asthma-related outcomes**

Regulation policies decreasing outdoor pollutants below the WHO thresholds possibly reduce the risk of the emergency department visits and hospitalization for asthma	Conditional recommendation
Interventions like Olympic Game restrictions possibly decrease the risk for outpatient visits, emergency department visits and hospitalizations for asthma	Conditional recommendation
Interventions like the COVID-19 lockdowns possibly decrease the risk for emergency department visits and hospitalizations for asthma	Conditional recommendation

3.4.3 | Justification

Very low certainty evidence showed that regulation policies or other interventions decreasing outdoor pollutants have an impact on the asthma-related outcomes. Although the importance of the mitigating outdoor air pollution is highly acknowledged, due to quality of available narrative evidence the GDG formulated a conditional recommendation. The EtD framework is presented in Table 11.

3.5 | Exposures and interventions not covered by the systematic review

This Guideline formulated recommendations only for the short-term exposure to outdoor pollutants covered by the WHO AQG 2021 and their impact on asthma-related outcomes. Nonetheless, the GDG acknowledges the danger and health burden of other exposures that were not covered in this Guideline. These include different nitrogen oxides besides NO_2, microplastics, phthalates, mercury, lead, ammonia, methane, polycyclic aromatic hydrocarbons, volatile organic compounds (VOCs) and other hazardous air pollutants.

The abundance and distribution of microplastic (MP) (<5 mm) has become a growing concern, particularly over the past decade.[122] Research to date has focused on water, soil and organism matrices but generally disregarded air. A recent review showed that the ambient air featured concentrations between <1 to >1000 microplastics/m^3 (outdoor) and <1 microplastic/m^3 to 1583 ± 1181 (mean)

TABLE 11 (A) Evidence-to-decision table assessing the impact of regulation policies and other implementations reducing exposure to outdoor pollutants on the ED visits and hospitalization for asthma. (B) Evidence-to-decision table assessing the impact of Olympic game restrictions on the outpatient visits, emergency care and hospitalizations for asthma. (C) Evidence-to-decision table assessing the impact of Covid-19 lockdowns the emergency care and hospitalizations for asthma.

A

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large	Varies		Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies		Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does net favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

B

	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large	Varies		Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies		Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does net favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

(Continues)

TABLE 11 (Continued)

B							
	Judgement						
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know
C							
	Judgement						
Problem (importance)	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large	Varies		Don't know
Undesirable effects	Large	Moderate	Small	Trivial	Varies		Don't know
Certainty of evidence	Very low	Low	Moderate	High			No studies included
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does net favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No studies included
Cost effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No studies included
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

Note: Yellow means response selected by the Panel.

microplastics/m^3 (indoor), consisting of polyethylene terephthalate, polyethylene and polypropylene.[123] Road dust concentrations varied between 2±2 and 477 microplastics/g (mean), consisting of polyvinyl chloride, polyethylene and polypropylene. Mean outdoor dust concentrations ranged from <1 microplastic/g (remote desert) to between 18 and 225 microplastics/g, comprised of polyethylene terephthalate, polyamide and polypropylene. Snow concentrations varied between 0.1 and 30,000 microplastics/L, containing polyethylene, polyamide and polypropylene. Similar to PM, inhaled MP damage the epithelial barrier and triggers inflammation, oxidative stress and cytotoxicity thus impacting asthma-related outcomes.[24,124] Also similar to PM, MP can reach to other tissues via the bloodstream. The negative health effects are not limited to the nature of the MP (e.g., chemical properties, shape and size) but they can also serve as vectors for different pathogens.[125] Sources of MP include outdoor dust, traffic, degradation of plastic in uncovered garbage bins and others.[124–126] Most studies on MP effects have been conducted in isolated cell cultures or in animal models, while human data are sparse.

Phthalates are ubiquitously present environmental contaminants and have been linked to adverse health effects, including increased risk of asthma-related adverse outcomes. Exposure occurs via inhalation, contaminated food and food containers, drinking water or via skin (cosmetics and personal care products). Air and dust are the most important mediums of inhalant exposure to phthalates. Globally, phthalates are distributed due to atmospheric transport and are associated with both gas and particle phase.[127] Measurements of the outdoor air concentrations of phthalates conducted at eight different sites across the Greater Toronto Area during 2016–2017 showed high levels (1200 pg/m^3) at sites characterized by high levels of urban and traffic activity.[128] The high concentration had a strong correlation with the ambient temperature. Exposure to phthalates may impact the respiratory microbiome.[129] In vivo and in vitro studies have revealed that phthalate exposure enhances respiratory sensitization, allergic responses and oxidative stress.[130] Epidemiological studies suggest phthalate exposure is associated with asthma outcomes.[131] Overall, the evidence for association between phthalate exposure and respiratory disease is weak and inconsistent. Therefore, thorough implementation in large populations is needed to enhance the overall understanding of the potential respiratory health risks of phthalate exposure.[132]

Heavy metals such as mercury and lead may adhere to fine particles (PMs or MPs) in the air and act as environmental allergens for asthma.[133] Heavy metals trigger the immune system and have significant pro-inflammatory effect.[134,135]

Several studies indicate that ammonia (NH_3) has a direct effect on the respiratory health including a reduced lung function, increased coughing and phlegm expulsion. Recent studies have indicated that agricultural NH_3 may directly influence the early onset of asthma in young children. NH_3 is also a substantial contributor to the $PM_{2.5}$ fraction, and it accounts for the formation of 30% and 50% of all $PM_{2.5}$ in the US and Europe, respectively.[136] Occupational exposure to NH_3, for example in poultry farms, may decrease lung function and increase airway hyper-reactivity and inflammation.[137–139]

Methane exposure originating from various sources, including agricultural activities, coal mining, as well as oil and gas production and transport, can also exacerbate asthma symptoms or induce asthma attacks. Further, it can contribute to the formation of ground-level O_3 and PM pollution thereby leading to worsening of asthma-related outcomes, especially in children.[140–142]

Polycyclic aromatic hydrocarbons (PAHs) are a group of hydrocarbons originated from the incomplete combustion of tobacco, wood, coal and fossil fuels. PAHs may be adsorbed on inhaled PM surface.[143] Their wide environmental distribution poses a potentially serious hazard for human exposure. In children, a significant association between PAH and wheeze was found.[144] Other studies found a negative association between lung function and PAHs exposure.[145–147]

Volatile organic compounds (VOCs) in urban areas are of great interest due to their significant role in forming ground-level O_3 and adverse public health effects. Most the outdoor VOCs are generated by traffic, biogenic emissions, oil and gas industries, agricultural activities and the energy sector. Trends over the past few years have shown a remarkable decrease in outdoor VOC emissions (e.g., 49% reduction in 2020 as compared with 1990) due to efforts made at the government level by devising regulations for on-road vehicle and engine emissions.[148] Currently, non-combustion sources such volatile chemical products (VCPs) contribute to a higher fraction of outdoor VOC emissions.[149] Besides the outdoor or occupational exposure ambient VOCs can infiltrate easily into indoor spaces such as buildings and residential houses and impact asthma-related outcomes.[150,151]

One of the great challenges of the modern world is the generation of waste and how to dispose of it in an environmentally correct manner. Unfortunately, about 50 per cent of the world's waste is not managed properly being discarded by open dumping and burning. When waste is disposed of in this manner, it releases harmful substances into the air. In LMIC workers, including children, are sometimes hired to collect, sort or dispose of waste in unsafe conditions. Small individual actions can make a big difference in keeping the air clean like separate waste correctly or direct consumed products, such as batteries, tires, light bulbs and medicines and their packaging, for recycling or appropriate final disposal. Proper waste management is part of the WHO's Urban Health Initiative.[152] Circular municipal waste management systems can significantly reduce emissions of greenhouse gases and air pollutants.[153]

The outdoor pollution challenge brought by chronic respiratory disease like asthma and chronic obstructive pulmonary disease (COPD) themselves is fourfold: (a) they are among the most common chronic diseases worldwide; (b) inhaled therapies are the major way of treatment for asthma and COPD patients; (c) there is insufficient control of asthma and COPD, and this is frequently associated with over-reliance on the reliever and with poor inhaler technique, increasing the emissions instead of proper delivery of medication to the lungs; and (d) there is significant HCPs lack awareness of the inhalers' carbon footprint, while on the regulatory side only the active pharmaceutical ingredients are evaluated for their environmental impact instead of the 'whole package' (e.g., hydrofluorocarbons contained in MDIs,

TABLE 12 Gaps in evidence for the impact of outdoor pollution on asthma-related outcomes and plans to address.

Gaps in evidence	Plan to address	Priority
Standardization in assessment tools, methodology and outcomes	Expert-based consensus validated in prospective trials	High
Infrastructures, technologies and human resources for sustainable research on environment, climate change and health	Well-designed and maintained population cohorts and related biobanks, research facilities capabilities, data science tools, transdisciplinary research	High
Understanding of the biological mechanisms of individual pollutants exposure impacting asthma pathogenesis (epithelial barrier, inflammation, airway hyper-reactivity and remodelling) and the mechanisms of individual resilience	Mechanistic studies on individual exposure followed by the exposomic approach building risk profiles Confirmation of risk profiles in population-based studies	High
Which pollutant is specifically associated which specific asthma outcome	Identify mode-of-action of specific pollutants—mechanistic studies	Medium
Timing of exposure associated with asthma-related outcomes	Age group exposure studies	High
Concentration of outdoor pollutant associated with asthma onset and asthma-related outcomes	Identify the minimum concentration needed to induce pathological changes within cells and tissues	High
Combined effects of outdoor pollution and other environmental stressors (e.g., indoor air pollution, climate change, allergens and viruses)	Exposomics and population-based studies	High
Individual and population risk profiles	Population-based studies Personalized risk assessment	High
Environmental health communication	Tailored educational programmes	High

carbon footprint of continuous production of new devices instead of recycling). The three principal types of inhalers are as follows: (a) pressurized metered-dose inhalers (pMDIs) used with or without holding chambers or spacers, (b) dry-powder inhalers (DPIs) and (c) soft mist inhalers (SMIs). The most common inhalers, the pMDIs, use hydrofluorocarbon propellants (HFC-134a and HFC-227ea), which are powerful greenhouse gases (GHG). MDIs are associated with a 10–40 times higher CO_2-footprint than GHG-free DPIs. The end of life of inhalers occurs through domestic disposal, return to pharmacies or recycling. Most of the domestic disposal goes to landfills, with a very limited proportion being incinerated or even less incinerated with energy recovery. This is in contrast with pharmacy disposal where devices are incinerated with or without energy disposal. Landfill disposal of pMDI devices with unused doses continue to release GHG, which persist in the atmosphere for up to 50 years. Unfortunately, <1% of inhaler devices are recycled every year worldwide. There are several steps to an eco-friendly approach in asthma and COPD management: (a) switching from MDIs to DPIs or SMIs; (b) strategies like maintenance and reliever therapy which uses combination reliever and ICS in one device (usually a DPI) or the anti-inflammatory reliever approach with ICS-formoterol can simplify therapy, improve asthma control and reduce GHG emissions; (c) conception of inhalers with dose counters to prevent waste, integrating whistles to optimize inhalation technique, making inhalers refillable, or optimizing materials for recycling and investment into new, lower GWP propellants; and (d) waste management options favouring recycling.[154]

We assessed the impact of complex regulation policies aiming at reducing outdoor pollutants. However, individual fast developing fields such as the new-energy vehicle industry setting records, including in heavily polluted countries like China or India, deserve further research.

3.6 | Gaps in knowledge and recommendations for future research and management pathways

Although much research on outdoor air pollution and asthma has been done, major gaps in our knowledge remain. A short summary of the identified gaps is presented in Table 12, together with plans to address them.

One of the most critical gaps is understanding the individual biological basis (e.g., genetic or epigenetic factors driving the resilience response) and the precise mechanisms by which each type of air pollutants and their combinations with other pollutants or with other components of the exposome contribute to the onset of asthma or to its severity.[155] Improved mechanistic understanding of the environmental-driven asthma endotypes is needed to develop targeted strategies to improve asthma-related outcomes in the context of outdoor pollution.[156,157]

Exposure to $PM_{2.5}$ and TRAP is associated with increased risk of new-onset asthma or asthma exacerbations, but it remains unclear which of the components of this particulate mix are the most responsible. NO_2, a relatively mild oxidant at ambient concentrations, is repeatedly noted in epidemiological studies as the pollutant with the most impact on asthma, but the reason is unclear. Also, polycyclic aromatic hydrocarbons are another class of pollutants where more information is needed.

Another key question is whether short-term peak exposures (e.g., 1 h) versus time-weighted averages over longer time periods (e.g., over several days) are associated with increased risk of adverse asthma outcomes. Many studies show a strong effect on the day after high-level pollutant exposure, rather than on the day of exposure.

Assessment of individual level exposure is primarily based on either distance from air quality monitoring stations or estimates from

models. Improved personal monitoring allowing individuals to assess their own exposure in the context of daily activities is essential for developing personal risk charts and tailored interventions.

The adverse effects of exposure to outdoor air pollutants might vary over the life span. Future research should address pathogenetic mechanisms specific for each age groups.[158] Prenatal exposures to pollutants might affect risk of disease later in life or in the next generation.[159,160]

The most challenging task for air pollution research is how to address the cumulative impact of exposure to a mixture of pollutants, other environmental stressors and biological substances.[1,161,162] Effective strategies to address this confounding are needed for epidemiological, mechanistic and intervention studies, such as prospective studies of risk of hospital admissions in relation to a more detailed measurement of each component of the exposure.

Climate change will lead to increases in ambient concentrations of pollutants, mainly O_3 (directly as a result of increased UV light catalysing the interaction of nitrogen oxides with VOCs) as well as NO_2 and $PM_{2.5}$ (released due to increased energy production or wildfires). Increased exposures to aeroallergens are also projected because of lengthened growing seasons and a possible increased production of pollen.[24,163,164] Improved understanding of the interactions of pollutants, other exposome components and adverse health effects will be needed to address the expected increased risk of asthma exacerbations in the context for example of climate change.[165,166] New information systems contribute to a better evaluation of the exposure and to a better information.[167] Studies on the impact of the exposome, covering all environmental exposures throughout an individual's life span, on the dysfunction of the epithelial barriers are needed to improve the understanding of epithelial barrier-related diseases such as asthma and raise awareness of the environmental insults that pose a threat to human health. The study of the exposome requires consideration of both the co-exposures and their changes over time, and as such requires high-quality data and software solutions combining precision immunology tools with the opportunity offered by major advances in data science.[167–172] As the exposome is both a broad and a recent concept, it is challenging to define or to introduce in a structured way. Thus, an approach to assist with clear definitions and a structured framework is needed for the wider scientific community and for public communication.[168] A more comprehensive model is the One Health approach, with a sharp focus on human, animal and environmental health interconnections. According to the One Health inhalant exposures to a wide range of allergens, infectious agents and pollutants occurring indoors and outdoors are heavily influenced by environmental health (air, water and soil quality) intermingled with animal health. These are further impacted by climate change, land use, urbanization, migration, overpopulation and many more. Thus, a coordinated response to address the underlying factors that contribute to the development of allergic diseases and asthma needs to focus on the environment, human and animal health altogether.[173,174]

Together with exposomic studies, better population studies are required to understand population health and its determinants.[8,175–178] Assuring public health faces challenging economical constrains together with societal norms and influences. Given these challenges, it is necessary to be integrated into national, regional and international health policies. Approaching health from a population perspective commits a nation to understanding and acting on the full array of factors that affect health. An effective intersectoral public health system is needed to achieve this goal. Thus, the governmental sector needs to work in partnership with academia and patients and consumers communities to create a better intersectoral public health system. Acknowledging that the greatest benefit is achieved by mitigation policies guided by population-attributable risk and by tailoring to differences in risk exposures and inequity in access to asthma diagnosis and care will help developing true population-based intervention strategies for mitigating the impact of outdoor pollution on asthma-related outcomes.[8,179–186] However, understanding and improving a population's health relies not only on understanding the population perspective but also on understanding the ecology of health and the interconnectedness of the biological, behavioural, physical and socioenvironmental domains.[162,163,187,188]

The need for monitoring and alert systems is rapidly growing and the economic support barely keeps pace.[62] Furthermore, with climate change effects, information about pollution levels and type of pollution should be combined with weather information (temperature, humidity, wind) and occurrence of events such as storms and wildfires in the vicinity, which impact on the level and type of pollution.

Regulatory pollution limits vary across countries and supports legally actionable evidence of air pollution, reinforcing conceptions of air quality being synonymous with the specified pollutants, monitoring methods and acceptable concentration thresholds. The release of the AQG 2021 by the WHO raises questions on the quality of the air pollution information offered to the public, what messages individuals receive through freely accessible air quality channels, how citizens are encouraged to act on this information, and whether access to this information is equal for all groups of populations.[189]

4 | RECOMMENDATIONS FOR HEALTHCARE PROFESSIONALS, POLICY MAKERS AND REGULATORS AND CITIZEN GROUPS

In alignment with the target audience of these guidelines the research evidence indicates the need to avoid being exposed to severely polluted environments and to be prepared for any asthma exacerbation in settings with heavy pollution.

For clinicians, the evidence informs their asthma management plan by aiming for optimal asthma control while evaluating the exposure risk and impact, tailor the measures to the type of pollutant and integrate in the context of co-exposures and choose the desired intervention by shared decision-making with the patient (Figure 2).

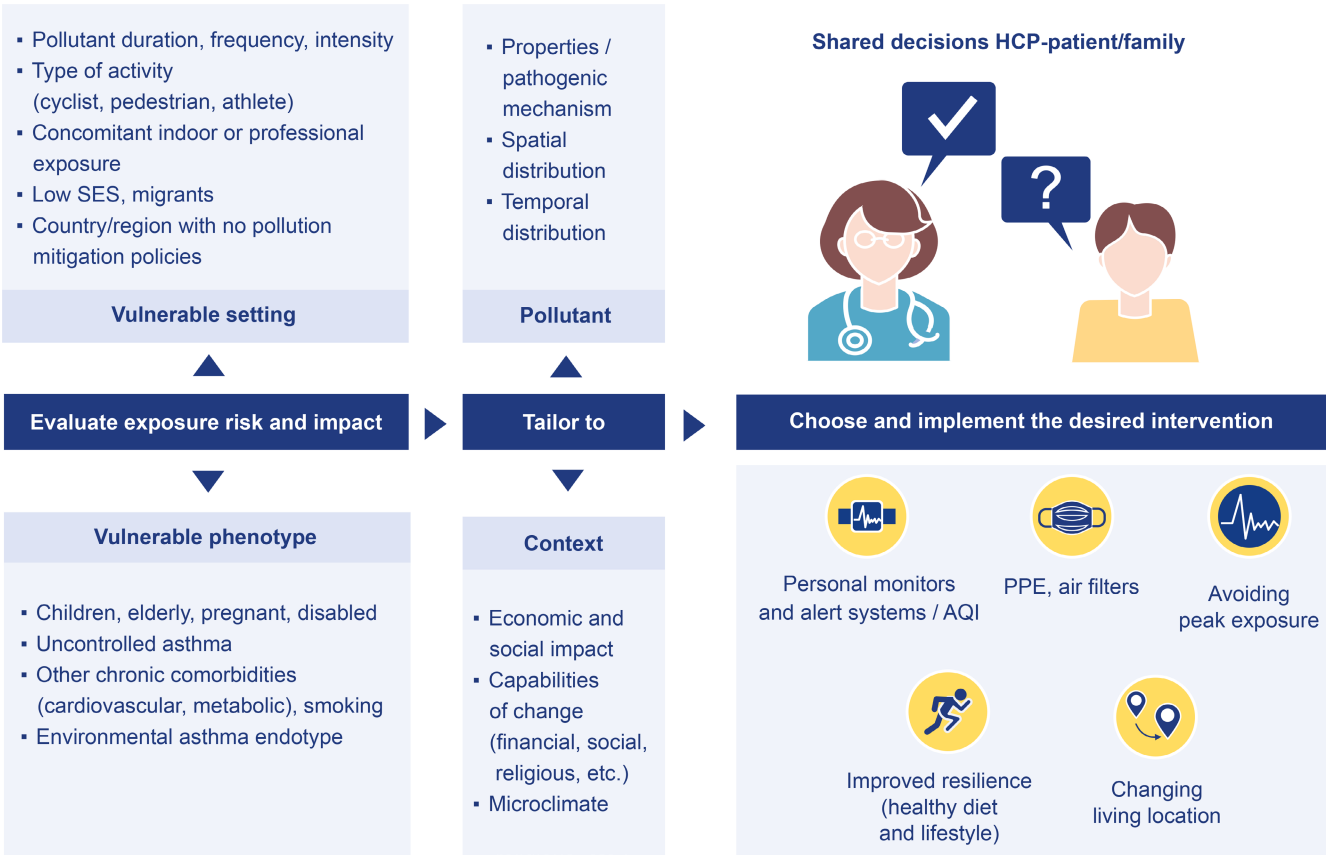

FIGURE 2 Outdoor pollution guidelines-informed asthma management plan. For healthcare professionals (HCP) aiming for optimal asthma control, the evidence and the recommendations provided by the EAACI guidelines inform their three-step asthma management plan. First, the outdoor pollutants' exposure risk and impact should be thoroughly evaluated, with a special focus on revealing vulnerable phenotypes and high-risk settings. In the second step, the HCP tailors the measures to the type of pollutant and to the context and integrates them in the context of co-exposures. In the third step, the by shared decision-making with the patient the desired intervention is chosen and implemented.

A similar tailored approach is recommended for advising an asthma patient on the risk of occupational exposure. Engagement with patient representatives for awareness raising, educating and advising patients, specifically the most susceptible and vulnerable patient groups is also recommended.

5 | RECOMMENDATIONS FOR POLICY MAKERS AND REGULATORS AND CITIZEN GROUPS

A list of policies by different governments and organizations is presented in Table 13. The aim of this EAACI guideline is to offer a blue-print for public policies that have the potential to make a tremendous impact on the health and quality of life of those living with asthma (Figure 3).

The current research evidence aims to support the decisions of policy makers on the outdoor pollution reduction plan, considering the potential benefits on preserving adults and children's health and on minimising their impact on patients suffering from chronic diseases. Scientific allergy and respiratory societies and patient associations, along with other stakeholders in the health sector, should increase their engagement and advocacy to raise awareness of clean air policies and on the implementation of the latest WHO AQG. Regulatory agencies and governments should adopt and implement strong measures to reduce emissions of outdoor air pollutants that cause or worsen asthma and contribute to climate change. Lowering thresholds of acceptable levels of outdoor air pollution and stricter enforcement of existing legislation is warranted. Reimbursement policies should cover mitigation measures and tools addressing the environmental triggers of asthma.

National, regional and international asthma programmes should develop a strategic plan to document the outdoor pollution problem, implement strategies and assess progress. These programmes should also ensure that they address environmental-driven asthma in underserved and disproportionately affected populations in their strategic plan and activities.

Healthcare education programmes at all levels should include environmental health strategies.

A wide range of tools that support decisions on air pollution, and more generally for sustainable human settlements and urban planning, has been developed and made available for users by WHO, US Environmental Protection Agency and European Environment Agency.[190–192] Smart home- or workplace-based asthma services

TABLE 13 Comparison of policies for increased air quality.

Country/region	Policy for regulating air quality	Aim	Asthma-specific interventions and programmes
European Union	Clean air policy package	Improved air quality and decreased health care costs by 2030	National Emission Ceilings Directive EU Ambient Air Quality Directives
United States	US EPA Clean Air Act	Sets limits on certain air pollutants	National Asthma Control Program; EXHALE (CDC) National Asthma Education and Prevention Program (NIH) Several non-federal government organizations (e.g., National Asthma Public Policy Agenda of the American Lung Association)
UK	Environment Act 2021	Sets legally binding targets in priority areas including air quality and limits for $PM_{2.5}$ pollution	Clean Air (Human Rights) Bill
AUSTRALIA	National Clean Air Agreement	Framework for local governments to identify and prioritize actions to maintain and improve air quality	National Asthma Strategy National Asthma Indicators
United Nations	Resolution 3/8 on Preventing Air Pollution	Adopt and implement key actions significantly improving air quality for Member States	

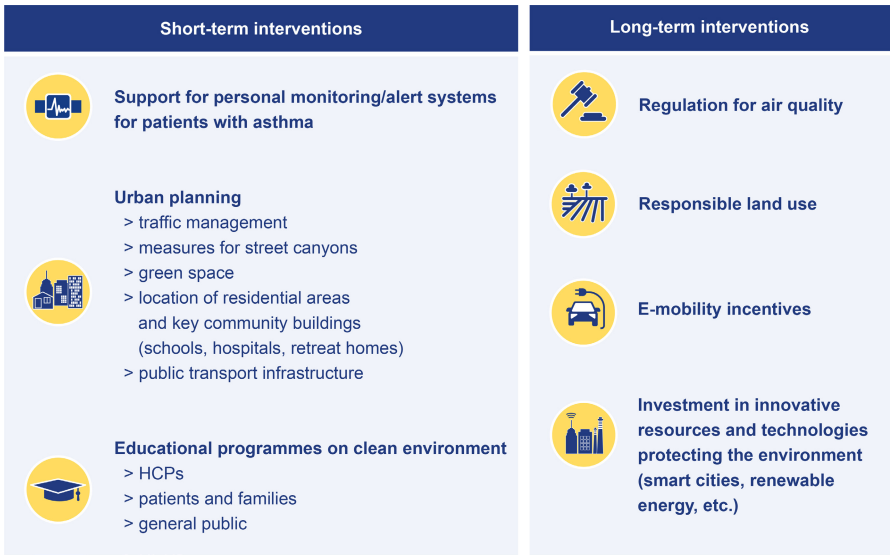

FIGURE 3 Integrating mitigation measures for outdoor pollution in the public policies. Mitigation measures can be either readily implemented or long-term interventions. Healthcare systems offering support for personal monitoring and alert system for patients with asthma can immediately optimize achieving and maintain asthma control. Smart urban planning can readily achieve important reductions in daily emissions and thus allow patients with asthma a normal life without avoidance of outdoor exposures. Academia should prioritize educational programmes tailored to healthcare professionals, patients and families and the general public. In the long-term regulations for air quality, responsible land use, promotion of e-mobility and investment in innovative resources and technologies can ensure more permanent clean environment with the hope of the reversal of the environmental-driven asthma endotypes and achievement of asthma remission.

that reduce or eliminate environmental asthma triggers, ingenious urban planning, green technology and e-mobility incentives are all excellent tools to achieve optimal air quality.

6 | CONCLUSION

The EAACI Guideline recommendations on the impact and mitigation of short-term exposure to outdoor pollutants on asthma-related outcomes summarize the available evidence included into SR and rates their certainty based on the GRADE approach. Recommendations were formulated for exposure to different single as well as for mixed air pollutants, such as TRAP, and for the implemented regulatory policies leading to decreased air pollution. The limits of exposure to major outdoor pollutants were based on the references from the AQG 2021 (WHO).

More detailed compared to the WHO AQG 2021 or the EU's AQD, the evidence focused on the impact of the pollutants on several asthma-related outcomes such as asthma exacerbations, lung function or asthma-related QoL. In addition, the EAACI Guideline

provides recommendations about multiple exposures that are not covered by the WHO AQG 2021.

Short-term exposure (up to 4 days) to specific air pollutants (CO, NO_2, O_3, $PM_{2.5}$, PM_{10} and SO_2) probably increases the risk of asthma-related hospital admissions, and to a lower extent asthma-related emergency department visits, with moderate certainty of evidence for specific time lags. There was limited evidence on the effects of TRAP and pesticides exposure as well as for the interventions to reduce emissions on asthma-related outcomes.

Due to the quality of included evidence (observational studies) and the overall low number of studies, conditional recommendations were formulated for all research questions. However, the GDG acknowledges the overall risk and burden of outdoor pollutants and their association with asthma-related outcomes. Interventions to reduce air pollution and the implementation of new and sustainable technologies are of great importance and should attract worldwide attention.

The EAACI Guideline on the impact and mitigation of short-term exposure to outdoor air pollutants on asthma-related outcomes is a tool to help decision-making for all involved parties. HCPs can help asthmatic patients to reduce their personal risk of being exposed to high levels of air pollution. Patients and healthy individuals, however, are encouraged to take advantage of this information to prevent increased hospitalization rates and improve quality of life. Policy makers can use translate these recommendations into legally actionable evidence.

AUTHOR CONTRIBUTIONS

Ioana Agache, Marek Jutel and Cezmi Akdis conceptualized the outline of the guideline and wrote the manuscript. All the other authors revised and approved final manuscript.

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CONFLICT OF INTEREST STATEMENT

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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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SUPPORTING INFORMATION

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

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