Long-term health effects of outdoor air pollution on asthma and respiratory symptoms: a systematic review and meta-analysis

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2023

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This thesis is submitted in partial fulfillment of the requirements for the degree of

Master of Philosophy in Global Health at the University of Bergen

(60 ECTS credits)

Centre for International Health

Faculty of Medicine

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University of Bergen, Norway

2023

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List of Abbreviations

WHO: World Health Organization

LMICs: Low-and middle-income countries

DALYs: Disability-adjusted life-years

PM: Particulate matter

COPD: Chronic obstructive pulmonary disease

NO_2: Nitrogen dioxide

ppm: Parts per million

CO: Carbon monoxide

O_3: Ozone

SO_2: Sulfur dioxide

BC: Black carbon

VOCs: Volatile organic compounds

AQG: Global air quality guidelines

ESCAPE: European Study of Cohorts for Air Pollution Effects

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

PECOT: Population Exposure Comparator Outcomes Timing

PECOS: Population Exposure Comparator Outcomes Study design

ROBINS-E: Risk of Bias in Non-randomized Studies of Exposure

CoE: Certainty of Evidence

GRADE: Grading of Recommendations Assessment, Development and Evaluation

RoB: Risk of Bias

CI: Confidence Interval

Acknowledgment

I am very grateful to my main supervisor Professor Ane Johannessen for her unwavering supervisory support in grooming me as an upcoming researcher and also for giving me the opportunity to attend the European Respiratory Society Congress in Barcelona, Spain in 2022 as her first master's student to participate in the congress. I am also grateful to her for my involvement in the Life- Greenness Air Pollution (Life-GAP) project as a scientific assistant. Special thanks to my co-supervisor Shanshan Xu for her support as the second reviewer, her assistance in the statistical analysis, and for drawing my attention to every detail of this review.

I would also like to acknowledge the contribution of the university librarian, Elisabeth Ebner, for her assistance with the electronic search strategies and suggestions for the relevant databases.

I am also thankful to my family of orientation, extended families, friends, and well-wishers who have prayed for me, encouraged me, and wished me well throughout this journey.

Lastly, I would like to express my sincere gratitude to my family of procreation for their sacrifices, love, patience, and understanding over the past two years of being in a different city. I hereby dedicate this piece of work to you my husband Arome, and my children Eny'Ojo, Ojonemile, and Ojonugwa. Above all, I am eternally grateful to the Trinity (God the Father, Son, and Holy Spirit).

Achenyo Peace Abbah

Masters in Global Health

(August 2021 to May 2023)

1 Introduction

Air pollution overview

The problems of modern outdoor air pollution can be traced back to the 1950s in London where accretion of air pollution particularly sulphur dioxide and smoke reaching 1,500 mg/m^3, led to a dramatic increase in the death rates of 4000 deaths in December 1952 (1, 2, 3). Afterward, extremely high levels of air pollution with subsequent adverse health effects were reported in New York City (about 400 deaths in 1963), Mexico City and Rio de Janeiro, Milan, Ankara, Melbourne, Tokyo, and Moscow (1).

Air pollution is ranked as the fourth largest risk factor for premature death worldwide (4). In particular, the low-and middle-income countries (LMICs) continue to experience high burdens of diseases attributed to air pollution (5). It was estimated that particulate matter ($PM_{2.5}$) exposure have caused 4.2 million deaths and 103.1 million disability-adjusted life-years (DALYs) (6).

Pollution occurs when substances that have negative effects on humans and other living organisms are introduced into the environment. Toxic pollutants are in the form of solids, liquids, or gases that cause a deterioration in the quality of the environment (1). The effect of air pollution greatly affects people, especially those dwelling in large urban areas, where road emission is a major contributor to the deterioration of air quality. Also, industrial accidents may lead to the transmission of toxic fog which can be deadly to the people living around such places (1).

World Health Organization (WHO) defined air pollution as the contamination of the outdoor or indoor environment by any biological, chemical or physical agent that changes the natural features of the atmosphere (7). Duan et al. (8), acknowledged that air pollution results from the complex mixture of particles, gases, and vapors that emanate from natural and synthetic sources and are formed through photochemical transformation processes. Outdoor air pollution can be described as the existence of one or more substances in the atmosphere with duration and concentrations above the natural limits (9). Exposure to outdoor air pollution can lead to damage to several organs and systems of the human body, thereby severely affecting health. The respiratory tract is particularly susceptible to pollutants because it has direct exposure to the outside environment (8), and when a person breathes in pollutants, it causes oxidative stress, inflammation, immunosuppression, and mutagenicity in the cells of the body, thus, affecting and potentially causing diseases in the lungs, heart, brain, and other organs (10). Indoor air pollution occurs when harmful pollutants such as particulate matter, carbon monoxide, and other pollutants are released inside the building for example through indoor fuel burning for heating and cooking (11). For this review, we will focus only on outdoor air pollution.

Sources of air pollution

The WHO (10) reported that about 50% of the outdoor air pollution is due to household air pollution being discharged into the environment. This is because smoke leaks from doors, windows, and house chimneys. A major, most widespread, and significant source of air pollution exposure is the burning of biomass fuel such as raw plant material, dung, charcoal, wood, and crop residues that are either used for cooking or heating (28).

It has been established that the emission of most environmental pollutants is done through the performance of large-scale human activities, for instance, usage of industrial machines, combustion engines, cars, and power-producing stations as shown in **Figure 1**.

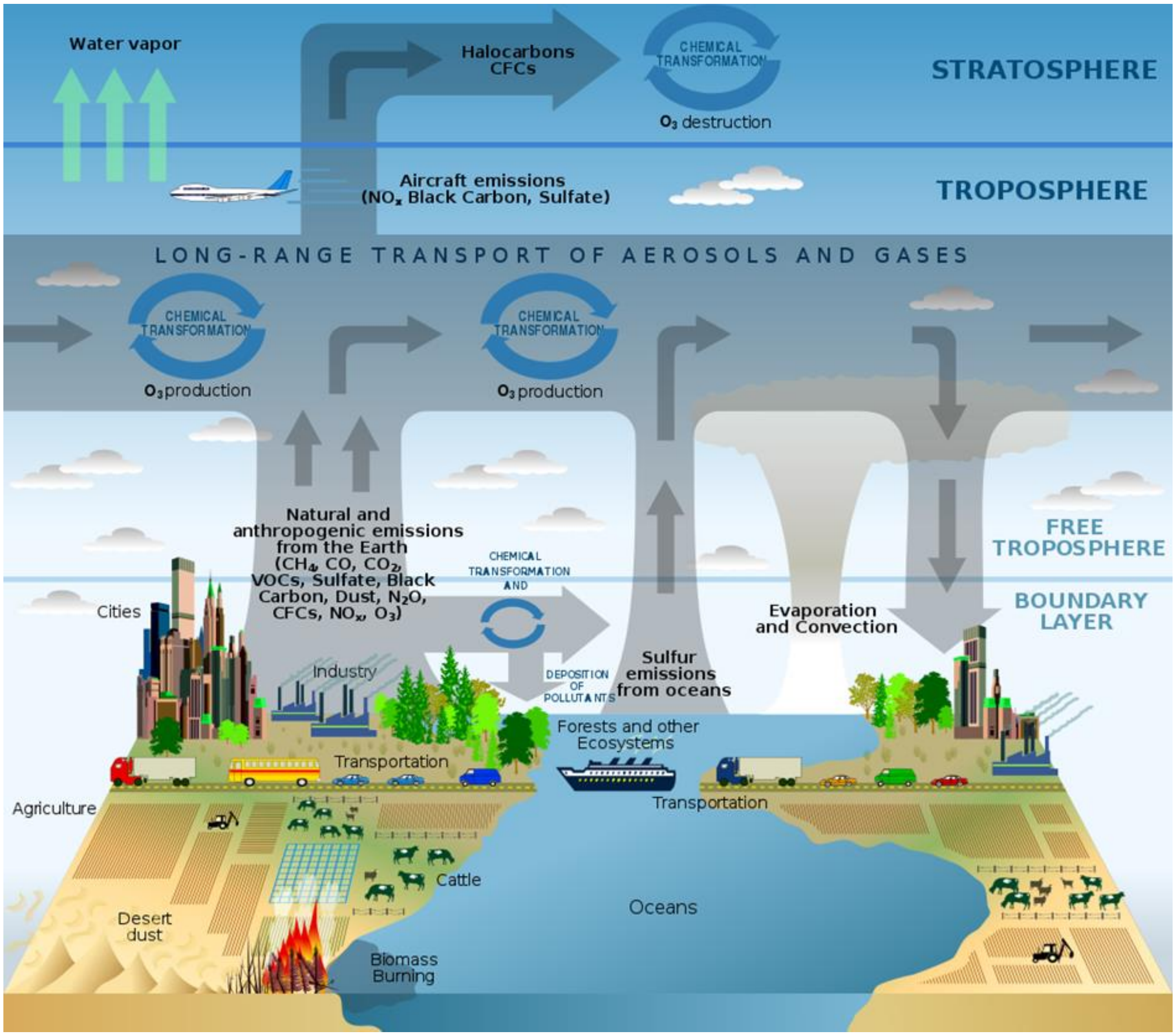

Figure 1: Composition diagram showing the evolution/cycles of various elements in Earth's atmosphere.

Retrieved from TROPOMI. Data products [Available from: http://www.tropomi.eu/data-products (12).

Exhaust emissions from cars are the major causes of recent air pollution (1, 13). This has been well explained by the recent WHO technical report and is also in line with the reports by the United States Environmental Protection Agency (EPA), emphasizing that emissions from vehicles can lead to adverse health effects of people who dwell or work near the roads (14, 15, 16).

According to Schultz et al. (17), outdoor air pollution is comprised by different intricate mixtures of compounds which differ in concentration depending on sources, geography, topography, wind direction, and speed, relative humidity, temperature, and ultraviolet radiation. Since these pollutants often come from the same sources and are spread alike, it may be challenging to differentiate the significance of one pollutant from the other when studying their health effects (17).

Based on the classification system of air pollution as identified by Manisalidis et al. (1), the four main sources are;

1. Major sources: pollutants that are emitted from power stations, refineries, petrochemicals, chemical and fertilizer industries, metallurgical and other industrial plants, and incineration from the community (1).
2. Mobile sources: automobiles, cars, railways, airways, and other types of vehicles (1).
3. Natural sources: physical disasters such as volcanic erosion, forest fire, and agricultural burning (1)
4. Indoor area sources: domestic cleaning activities, printing shops, dry cleaners, and petrol stations (1).

Health effects of air pollution

Long-term consequences of air pollution are often related to the onset of chronic diseases and conditions and may have a lasting impairing effect on both individuals and society. Such health problems can be respiratory diseases, cardiovascular diseases, different types of cancers, and other disorders such as sense of smell impairment and irritation in the eyes, nose, and throat (1, 4, 7, 8, 21, 24, 30). For humans, health effects of air pollution depend on the type of pollutant, the duration and level of exposure, and other factors such as individual health risks and the cumulative impacts of several pollutants or stressors (4). **Figure 2** below shows an overview of how pollutants such as particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), and black carbon (BC) cause negative impact on health.

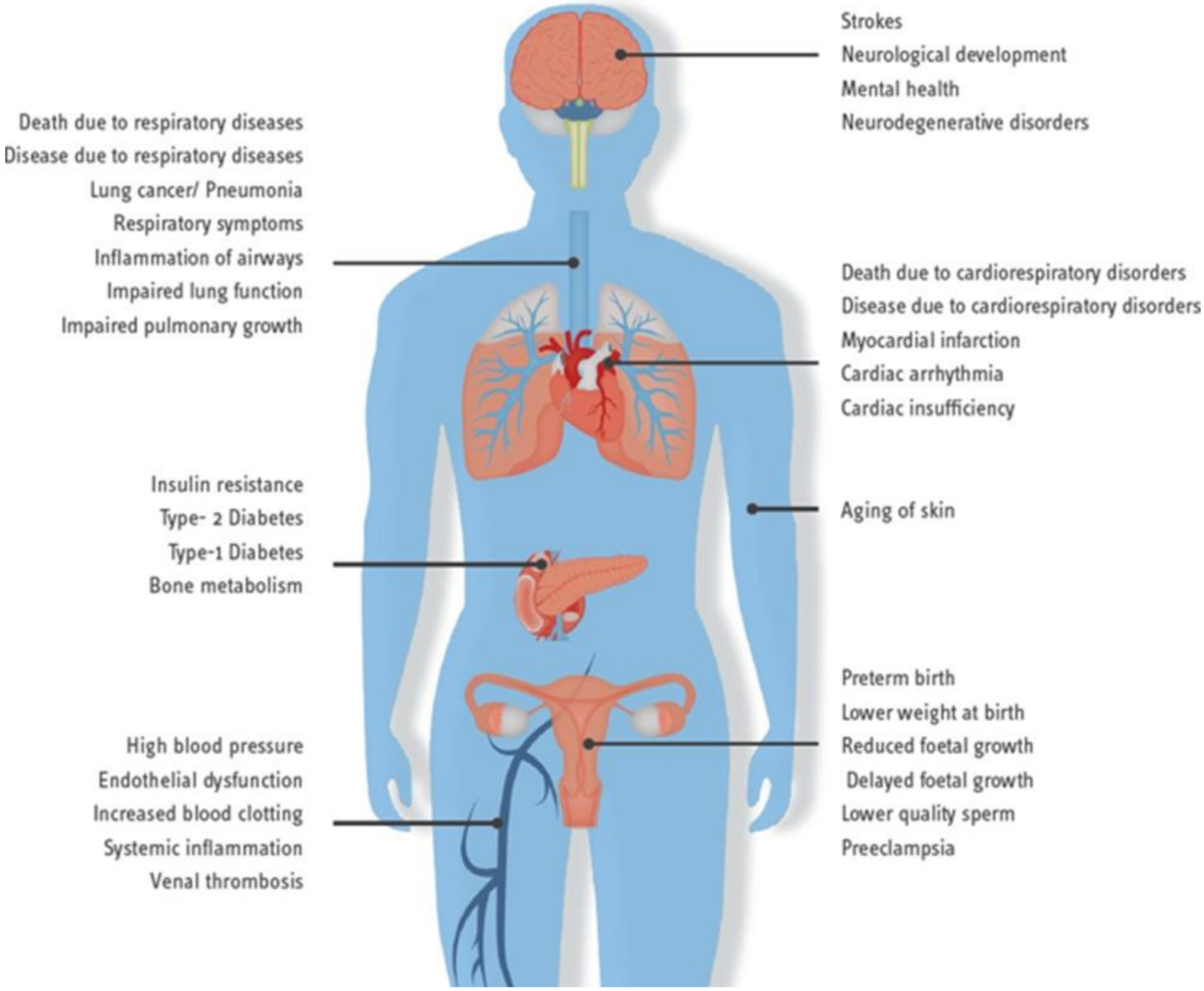

Figure 2: Overview of the health effects of air pollutants in the human body

Retrieved from Peters et al., from the European Respiratory Society: The Health Impact of Air Pollution. 2019. https://ers.app.box.com/s/81rilw1uyrj8kv24caowsy2hf7dv8nuz (18).

Asthma and respiratory symptoms

The term asthma has been defined in the paper. Guarnieri and Balmes (19) identified a major significant contributor to asthma to be urbanization which is closely linked to higher levels of outdoor air pollution. Furthermore, there is every likelihood for the global burden of asthma to increase due to ongoing rapid growth in population which is accompanied by increased outdoor air pollution in several urban areas in the developing countries especially China, India, and Southeast Asia.

It is challenging to figure out a particular, direct cause for asthma, but WHO (20) has identified certain factors that play a role in increasing the risk of asthma development.

- Genetic factor: a higher likelihood for the development of asthma if a close family member such as a parent or sibling has asthma.
- Allergic conditions such as eczema and rhinitis
- Multiple lifestyle factors linked with urbanization such as stress, lack of exercise, tobacco smoke, unhealthy diets.
- Some events or conditions during early life such as low birth weight, pre-mature birth, exposure to tobacco smoke and other sources of air pollution, viral respiratory infections.
- Exposure to a range of environmental allergens and irritants such as outdoor and indoor air pollution, moulds, house dust mites, and workplace exposure to chemicals, dusts, or fumes.
- Overweight and obesity.

A study conducted by Orellano et al. (21) showed that air pollution from NO_2, and PM may increase incidence, prevalence, hospitalizations, or worsening asthma symptoms. Exposure to fine particles has been reported to have caused respiratory symptoms (such as wheeze, cough, and phlegm), reduced pulmonary function, and increased airway inflammation and responsiveness (22, 23). In the present study, asthma and respiratory symptoms were selected as health outcomes associated.

Types of air pollutants

Diverse pollutants exist in the atmosphere, or on the ground but the pollutants that pose the strongest public health concerns are particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (24). For this review black carbon (BC), nitrogen dioxide (NO_2), and particulate matter- $PM_{2.5}$ and PM_{10} were selected as the pollutants of interest.

Particulate matter (PM)

PM is a complex heterogeneous combination of soot, dirt, smoke, and liquid droplets from both natural and man-made sources. The respiratory system is normally the first point of entry for PM into the body even though particles are seen in several organs (25).

PM are very small particles that consist of mineral dust, black carbon, water, nitrates, sulphate, ammonia, and sodium chloride which are suspended in the air we breathe in (26).

PM can be either primary or secondary depending on the mode it is discharged into the environment. Primary particles are imported into the atmosphere directly from their sources such as combustion, road transport, and wind-blown soils. Secondary PM is due to chemical reactions among various primary particulates such as nitrogen dioxides, volatile organic compounds (VOCs), sulfur dioxides (SO_2), and ammonia (27). Comparing primary PM to secondary PM, the chemical mechanisms involved in the composition of secondary PM are rather slow and thus, their persistence in the atmosphere is protracted (25, 28).

PM is classified based on the aerodynamic diameter it has significance for, especially at the point of deposition when breathed in. For instance as shown in **Figure 3** aerodynamic diameter of 2.5-10 μm of coarse PM is deposited primarily in the nose and broad conducting airways while $PM_{2.5}$ also known as fine PM is deposited everywhere in the respiratory tract and specifically in narrow alveoli and lower airways (19). Findings by Manisalidis et al. (1) show, in line with other epidemiological studies, that an association exist between PM and harmful health effects in both a short-term and long-term perspective. Due to the various chemical compositions and different ways of penetration in to the respiratory tract, the health impact of fine and coarse particles may vary (29). Park et al., (30) has pointed out that the size of the PM particles significantly determines their impact on airway inflammation. There is a negative relationship between the size of the PM and its level of toxicity in the lungs. The smaller the size of PM, the more adverse effect it will have. Another point worth taking note of by Duan et al., (8) is that PM can ingest other fungi, allergens, dust mites, microorganisms, and other pathogenic agents in the air which leads to more severe damage to the human body. Most existing studies focus on particulate matter (26) because they are the most significant source of health risks especially fine particulate matter since they are able to penetrate deep into the lungs, the bloodstreams, and travel to organs causing systemic damages to tissues and cells (10).

PM_{10} are particles up to 10 μm in aerodynamic diameter which are coarse (31) and primarily accrues in the upper respiratory tract, for example larynx, pharynx, and nasal cavity (8). PM_{10} after inhalation can penetrate the lungs (1). It is comprised mainly of crustal material, sea salt, and biological material (29).

$PM_{2.5}$ are fine particles with diameters 2.5 micrometers or less (1). $PM_{2.5}$ is also known as respirable particles because they have the ability to penetrate into the alveolar gas in the lungs and enter the bloodstream where they move to other parts of the body to cause potential harm to the heart, brain, and other organs (28).

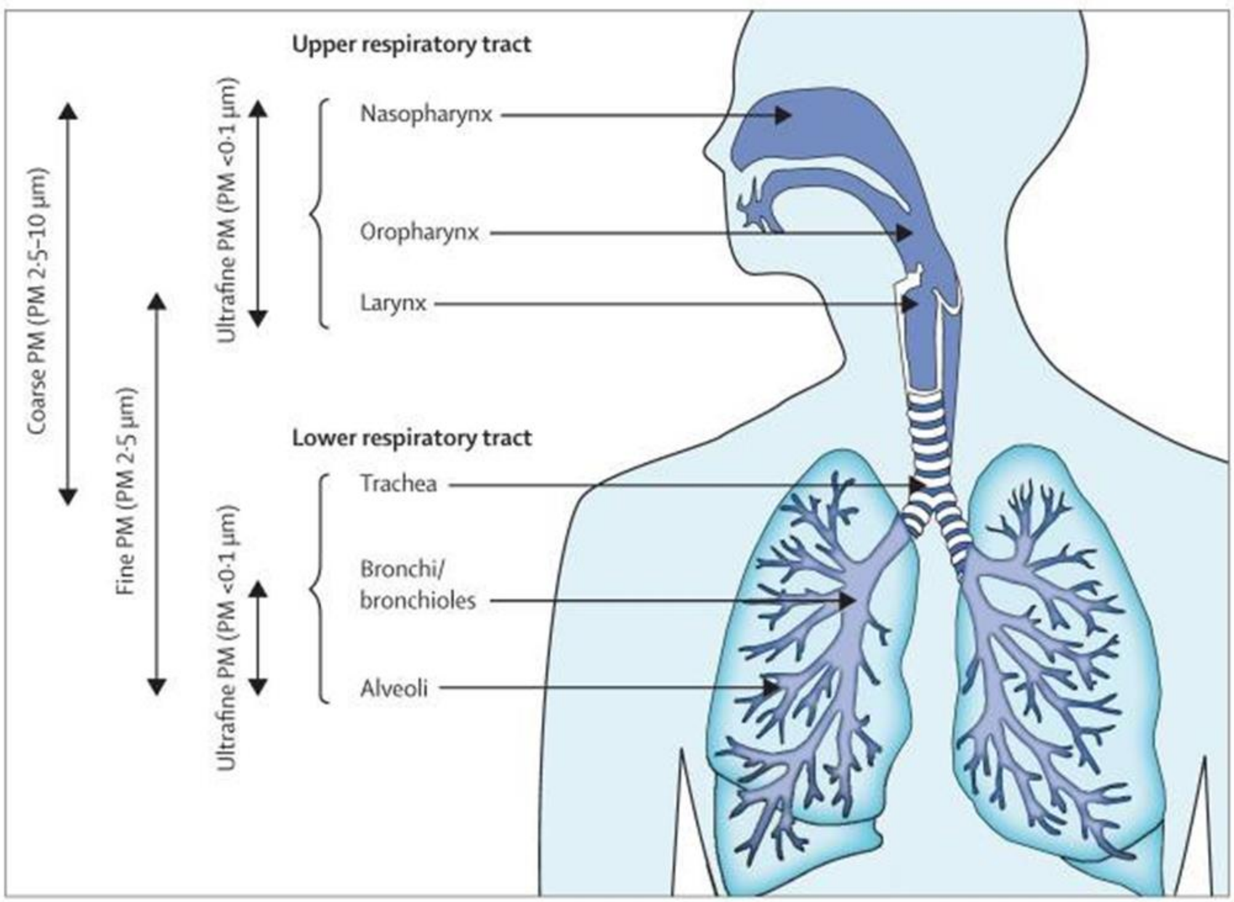

Figure 3: Compartmental deposition of particulate matter

Retrieved from Guarnieri M, Balmes JR. Outdoor air pollution and asthma. The Lancet. 2014;383(9928):1581-92 (19).

Black carbon (BC)

Black carbon is a component of fine particulate matter, a powerful warming agent in the atmosphere, and a major contributor to regional environmental disruption as well as an accelerator in the melting of glaciers (10). WHO (32) has defined black carbon as a dark, light-absorbing element of aerosols that has two parts of elemental carbon, that is the char-elemental carbon and soot-elemental carbon that are acquired from different combustion sources. Major sources of black carbon especially in the cities are vehicle-related traffic from diesel-driven vehicles and domestic burning of wood or coal, and open biomass-burning. Ågren (33) was of the opinion that if people's exposure to black carbon is reduced, the adverse health effects linked to $PM_{2.5}$ would be reduced.

Nitrogen dioxide (NO_2)

NO_2 is usually produced from the process of combustion particularly in relation to transport, heating, and power generation (24, 34). Irritation of the airways and aggravation of the respiratory system may occur with inhalation of nitrogen dioxide. The characteristics of nitrogen dioxide include solubility in water, strong oxidant and reddish-brown color (10). Stieb et al. (35) pointed out that NO_2 is a generally known marker of traffic-related urban air pollution and also mirrors combustion in air from sources such as fossil fuel and industry powered electric power generating stations. It was also noted in their study that during the past 15-20 years, NO_2 outdoor concentrations have reduced markedly in Europe, Japan, North America, and South Korea whereas, in other parts of the world, high levels of NO_2 concentrations are still on the increase.

WHO air quality guidelines and response to air pollution

The WHO Global air quality guidelines (AQG) have been largely used as a point of reference to assist decision-makers all around the world put in place standards and goal for the management of air quality (36). These guidelines offer global recommendation on thresholds and limits for important air pollutants that pose health risks. Although many countries have implemented legislation and public health interventions to reduce the emission of ambient air pollutants over the past decades, more than 99% of the world population still live in places where air quality does not meet the recently launched WHO 2021 air quality guideline (37). The WHO 2021 guidelines recommend annual average concentration of 5µg/m^3, 15 µg/m^3 and 10 µg/m^3 for $PM_{2.5}$, PM_{10} and NO_2 , respectively (38).

So far, WHO has put several measures in place to combat the growing problems of air pollution. These include the development and implementation of strategies to raise awareness on the health risks due to air pollution exposure, in addition to available solutions that can be used to alleviate the risks of exposure to air pollution (39). Another response by WHO is monitoring and reporting on global trends and changes in health outcomes in relation to measures taken to tackle air pollution at the national, regional and global levels (39).

Context of air pollution in LMICs

This systematic review used the definition of LMICs from the World Bank Classification (5).

Air pollution problems are more severe in LMICs because of overpopulation and uncontrolled urbanization, and rapid ongoing industrialization (1, 40). Challenges with poor air quality are particularly severe in regions with social discrepancies and inadequate or no information on sustainable management of the environment (1).

As shown in **Figure 4** most of the population in LMICs are exposed to higher levels of $PM_{2.5}$ than high-income countries (HICs). However, despite these high exposures, there is a striking lack of literature from the African continent on outdoor air pollution. This is consistent with the findings of Katoto et al., (41, 42) that there is no sufficient documentation on the degree of the attributable risk of outdoor air pollution in LMICs.

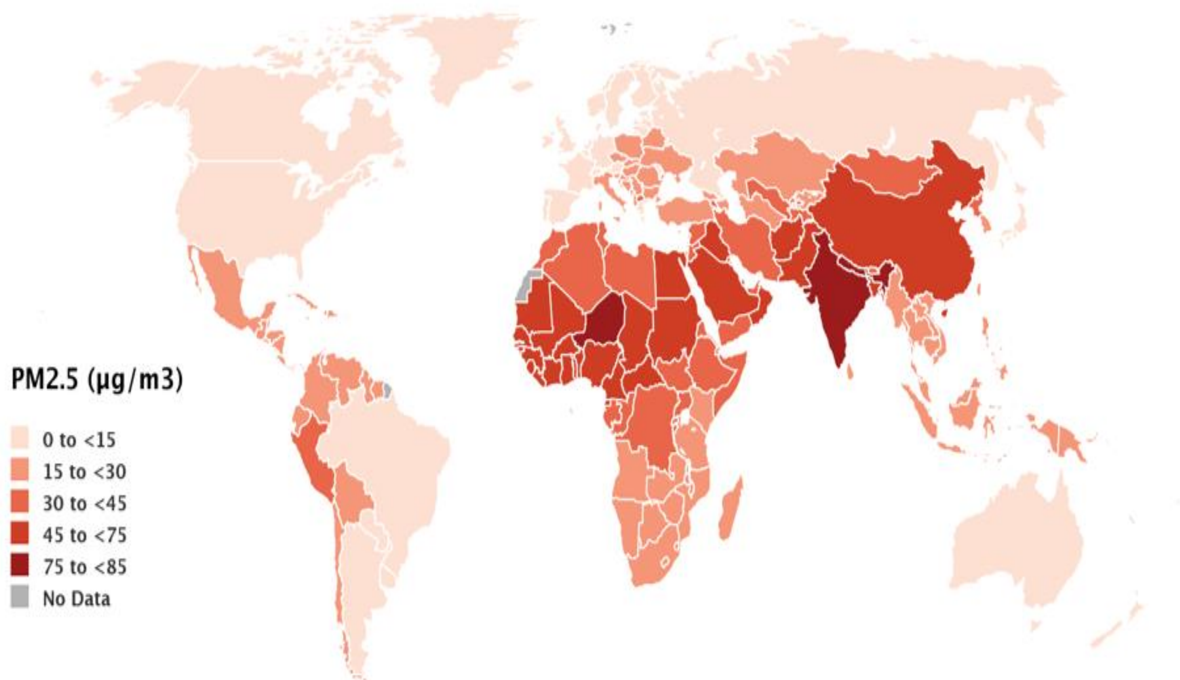

Figure 4: Global distribution of population weighted annual $PM_{2.5}$ concentrations for 2019 (HEI, 2020).

Figure produced from https: //www.stateofglobalair.org/data/#/air/map (last access: 10 December 2021) (43).

Lack of epidemiological studies of air pollution and respiratory health in LMICs

The epidemiological studies of exposure to air pollution and respiratory health in LMICs are limited. Both air pollution burden and asthma disease burden are highest in LMICs, but although some studies exist, systematic overviews from LMICs are lacking, in particular for adult populations (44, 45, 46, 47). As emphasized also in the introduction of the systematic review paper which constitutes the core of the master thesis, an overview of air pollution in relation to asthma in LMICs could be an important tool to identifying knowledge gaps where more original research studies are needed.

2 Main aim

The main aim of this study is to explore the association between long-term health effects of exposure to outdoor air pollution and asthma and respiratory symptoms among adults in LMICs. This systematic review is written as a scientific paper, targeted towards the Environmental Research Journal.

Specific objectives

1. To determine the air pollution sources that are most prevalent in LMICs.
2. To identify the respiratory health consequences of long-term outdoor air pollution exposure in adults in LMICs.
3. To examine the importance of different air pollutants such as $PM_{2.5}$, PM_{10}, NO_2, and black carbon in causing these respiratory health consequences.

3 Methods

As mentioned in the paper, this systematic review and meta-analysis was conducted according to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (48). For a better understanding and to provide detailed explanation for each reporting item on the checklist, we used the PRISMA 2020 Explanation and Elaboration (49) as a guide. In addition to registering the study protocol in advance in International Prospective Register of Systematic Reviews (PROSPERO- CRD42022311326), we also wrote a protocol paper which has received a minor revision decision from PLOS ONE and recently been revised and re-submitted accordingly. A final decision from PLOS ONE is expected shortly. The response letter to reviewers' comments can be found in Appendix 8.

Using PECOT to define the research question.

An important area to be given consideration before embarking any research is the formulation of research question which aims to examine an existing ambiguity in areas of concern, pointing to a need for study (50, 51). Establishing a good research question is one of the first crucial steps in the research process particularly in the areas of health and social research where the systematic formation of knowledge can be employed to improve, strengthen, maintain, and/or protect the health of individuals and populations (50).

As suggested by Ratan et al. (50) and Tawafik et al. (51), the research question of systematic review and meta-analysis like every other study design should be feasible, interesting, novel, ethical, and relevant (FINER) as well as manageable, appropriate, with potential value and systematic [FINERMAPS according to Ratan et al. (50)]. With regards to this, the approach of describing the Population (animal species inclusive), Exposure, Comparator, Outcomes, and Timing (PECOT) as pillars of the research question is widely acknowledged to evaluate the association between exposures and outcomes (52). PECOT further describes the study design or the criteria for inclusion and exclusion for a review (52). In addition, the PECOT provides the framework from which studies are identified and selected for inclusion (53).

Schaefer and Myers (54), Morgan et al. (52), and Riva et al. (55) explicitly defined PECOT as:

P – Population: the population (human populations and animal species inclusive) one aims to recruit in the study

E – Exposure: what the study population is exposed to.

C – Comparator: the reference or control group that is non-exposed or exposed to concentrations below the level that causes the health effects of the exposure.

O – Outcome: the adverse effects that one hypothesizes may happen due to the exposure

T – Timing: the duration of the study period.

This review used PECOT mainly as described above but with the timing (T) integrated into the population, and an S added for "Study design", formulating it into a PECOS framework. This has been done previously by Zheng et al., (56), Dimala et al., (57), and Boogaard et al., (58), and we chose this framework for our review because it explicitly describes each component of the research question. Using PECOS, the following research question was formulated:

Does long-term exposure to air pollution increase the risk of asthma and respiratory symptoms among adults in LMICs as compared to adults with relatively low levels of exposure to air pollution?

Eligibility criteria

Eligibility criteria are conducted according to the PECOT approach, study design, and date. Inclusion and exclusion criteria for the systematic review in this thesis are presented in **Box 1** in the paper. The most important exclusion criteria were no relation with the topic of interest, duplicates, full texts unavailability, or abstract-only papers. Inclusion criteria entailed studies on the pre-defined target population, exposure, and comparison of outcomes across different levels of exposure.

Assessment of risk of bias

Search strategy, data management and screening, and data extraction is described in the systematic review paper. The quality assessment using the Risk of Bias in Non-randomized Studies of Exposure (ROBINS-E) is also briefly described in the paper.

A more thorough description on how the overall judgement is obtained in ROBINSE-E and the algorithm for reaching the judgement of this tool is displayed in Table 1 & Table 2 below.

Table 1: ROBINS-E judgement and interpretations

Judgement	Interpretation	How it is reached
Low risk of bias	There is little or no concern about bias regarding this domain	Low risk of bias except for concerns about residual confounding in Domain 1 and Low risk of bias in all other domains
Moderate risk of bias(some concerns)	There is some concern about bias regarding this domain, although it is not clear that there is an important risk of bias	At least one domain is at Some concerns, but no domains are at High risk of bias or very high risk of bias

High risk of bias	The study has some important problems in this domain: characteristics of the study give rise to a high risk of bias	At least one domain is at High risk of bias, but no domains are at Very high risk of bias OR Several domains are at Some concerns, leading to an additive judgement of High risk of bias
Very high risk of bias	The study is very problematic in this domain: characteristics of the study give rise to a very high risk of bias	At least one domain is at Very high risk of bias OR Several domains are at High risk of bias, leading to an additive judgement of Very high risk of bias

Table 2: Algorithm for reaching judgement of whether bias threatens the conclusions.

Judgement	**How it is reached**
Yes	*Yes* in any domains
No	*No* in any domains
Can’t tell	At least one domain is *Can’t tell*, but no domains are *Yes*

Table 1 & Table 2 were retrieved from ROBINS-E Development Group led by Higgins et al., (59).

Meta-analysis

As far back as in 1930s, meta-analytical methods were used but in 1976, a researcher named Glass officially formed the term *meta-analysis* (60). Meta is a Greek word that means “after” or “beyond”; a meta-analysis is an “analysis of analyses”(61). Due to the continuous and increasing large amounts of new information emerging and being published, it has become unfeasible for healthcare practitioners to study and assess all accessible data in the healthcare sector. Furthermore, research findings from individual studies are usually not sufficient to draw clear conclusions. Hence, there is great need for an overview of the best evidence-based healthcare literature and this can be found in meta-analyses (61). Meta-analysis is defined as a method using mathematical procedure to combine and summarize the findings of a particular outcome that are extracted from analogous empirical studies (49, 60, 61). Lee (61) further pointed out that a meta-analysis is an objective, quantitative synthesis of study results that raises the statistical power and precision for effect estimates through the combination of existing findings. The issue of limited sample sizes and insufficient statistical power are consequently overcome.

As described by Cheung and Vijayakumar (62) and Lee (61), a meta-analysis merges the effect sizes of the included studies by weighting the data in accord with the diverse amounts of data in each study, using one of two statistical methods. On one hand, the fixed effect model infers that all of the studies in the meta-analysis have one true effect size and the observed variation amongst studies is due to sampling errors or chance. The fixed effect model evaluates only intra-study sampling errors, that is, within-study variation. On the other hand, the random effect model assumes that various studies display considerate diversification, and the true effect size might range between studies. It also evaluates both intra-study sampling errors and inter-study variance, that is, between-study variation (61). Given the explicit description of meta-analysis models, the choice of which model to use is dependent on the presence or absence of heterogeneity. A fixed effect model is used if heterogeneity is absent, that is heterogeneity $p \geq 0.10$ while a random effect model is recommended when there is a presence of heterogeneity, that is, the heterogeneity is significant ($p < 0.10$) (61).

With the understanding of which model to use as described by Lee above, the DerSimonian and Laird random-effects methods for meta-analysis was employed in the present thesis. This is in line with other systematic reviews and meta-analyses related to this topic of interest (29, 30, 35, 63, 64). DerSimonian and Laird random effects model has been known to be the simplest and most widely used method for fitting the random effects model for meta-analysis (65).

Heterogeneity

An important aim of a meta-analysis is to evaluate the presence of heterogeneity amidst primary studies and scrutinize the variance in the findings of the various studies. The degree of dissimilarity in the individual study findings is meta-analysis heterogeneity (61). The heterogeneity test assesses the null hypothesis, that there are no changes in the results of the primary studies. Lee (61) highlighted two major statistical tests that have been formulated to find and measure heterogeneity in meta-analysis.

- The Cochran's Q test is used to resolve whether significant differences are seen between primary studies or if the variation observed is because of chance. The Cochran's Q-value is calculated as the sum of the squared deviations of the estimate of each study from the overall estimate and comparing it afterwards with a chi-square distribution with κ-1 degrees of freedom (df), where κ represents the number of studies (61). Lee (61) further noted that when the meta-analysis involves only a few studies, there may be unreliability in the Q test. So, a significance p-level of $p < 0.10$ instead of the traditional 0.05 has been set to account for low statistical power and insensitivity in the Cochran's Q test.

- The I^2 value is another generally used method for testing heterogeneity, it measures the impact of heterogeneity and is not dependent on the number of studies or the type of outcome data. The I^2 values vary between 0% and 100%, and show the proportion of inter-study variability that is linked to heterogeneity instead of chance (61). The formula is [$I^2 = 100\% \times (Q - df)/Q$]. I^2 value of 25% is considered as low, 50% is moderate while 75% is high (29, 61). This implies that if the P values were less than 0.10 in the Q-test and/or the I^2 index was above 75%, then the pooled analysis will be regarded to be significantly heterogeneous (21).

Publication Bias

Lee (61) defined publication bias as overestimate of the "real effect degree" of studies. Studies that have positive effects are more often published than those that do not have positive effects, and studies that show no significant findings often remain unpublished. Andrade (60) identified that one of the ways to pinpoint the potential presence of publication bias is asymmetry in a funnel plot. A funnel plot is a scatter plot with the x-axis showing the effect size and the y-axis shows the measure of study precision or sample size. The funnel plot is used graphically where at the bottom of the graph, the effect estimates of small studies will scatter usually across the base of the plot while the distribution of the larger studies will be narrower usually around the top of the plot as described (66). When there is no publication bias, a symmetrical inverted funnel is produced on the funnel plot where the included studies have scattered on both sides of the overall effect line. Whereas, severe asymmetry to either side shows that publication bias might be present (66). As simple as the funnel plot method may be, the challenge is to decipher the plot when the number of studies is small (61). With the shortcomings of the funnel plots which need a range of studies of different sizes and include subjective judgments, publication bias can alternatively be assessed through other techniques, for instance the Egger's linear regression test. The Egger's linear regression test measures funnel plot asymmetry using a natural logarithm scale of odds ratios. It also assesses whether the intercept diverges substantially from zero in a regression of the standardized effect estimates against their precision (61). For this review, we used the Egger's linear regression test due to the small number of included studies for meta-analysis.

Analysis

Descriptive analysis

We conducted a narrative synthesis of the findings from the included studies. We structured the narrative synthesis by describing the studies according to the study design; characteristics of the target population such as age, sex, educational level, socioeconomic status; type of air pollutants; and type of respiratory health outcomes.

Statistical analysis

We pooled the results of the included studies using Random-effects DerSimonian-Laird model in the Stata software.

Evaluation of certainty of evidence

Following a detailed description of the certainty of evidence (CoE) in the paper, the overall rating of CoE as described by Orellano et al. (64) below was used in judging each pollutant exposure and outcome for the included studies.

- High: means there is unlikely change in the effect estimate given further studies.
- Moderate: a certain likelihood in change of the effect estimate given further studies.
- Low: further studies are very likely to cause a change in the effect estimate.
- Very low: high uncertainty in the effect estimate.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is defined as 'a systematic, and transparent framework for assessing and communicating the certainty of the available evidence used in decision making in healthcare and health-related disciplines' (67). The assessments for GRADE domains were mainly evaluated from the results of the risk of bias (RoB), heterogeneity, and publication bias analyses which were previously described here in the 'Methods section'. We adopted the reasons for both downgrade and upgrade as explicitly described by Chen et al., (29), Orellano et al., (63) and Orellano et al., (64). Upgrading indicates that we trust the results of the study more, and downgrading indicates we mean we trust the results of the study less.

Reasons for downgrade

Limitations in studies: The certainty of evidence (CoE) was downgraded with one or two levels if serious or very serious risk of bias was present in studies that had a substantial weight in the meta-analysis. If high risk of bias studies disagrees in effect size from low/moderate risk of bias studies, consideration should be given to rule out high risk of bias studies from the meta-analysis.

Indirectness: The CoE was downgraded if the included studies did not answer the PECOS question.

Inconsistency: if serious heterogeneity was detected, then the CoE was downgraded. For instance, if on one hand there were studies in the body of evidence that present an adverse effect and on the other hand, studies that also present a preventive effect, some heterogeneity is anticipated due to the likely differences in the various characteristics of the studies.

Imprecision: The CoE was downgraded if results are imprecise, for instance, when studies include few participants and few events and hence have a wide confidence interval (CI) around the effect estimate (68).

Publication bias: The CoE was downgraded if publication bias was found either by visual inspection of the funnel plot or through the Egger's test.

Reasons for upgrade

Large effect size: The CoE was upgraded if the pooled effect size was large or very large.

Confounding domain: The CoE was upgraded if all plausible confounding shifted the relative risk of the main exposure towards the null.

Concentration-response gradient: The CoE was upgraded if there was a concentration-response relationship between exposure and outcomes, either linearly or non-linearly.

Ethics approval and consent to participate.

This systematic review does not require ethical approval as it involves a synthesis of data collected from different primary studies. No primary data collection from patients was done for this systematic review.

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Target journal: Environmental Research

The format of academic paper was prepared according to the requirements of the journal.

5 Academic Paper

Long-term health effects of outdoor air pollution on asthma and respiratory symptoms: a systematic review and meta-analysis

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Abstract

Background: Several epidemiological studies have examined the risk of asthma and respiratory diseases in association with long-term exposure to outdoor air pollution. However, little is known regarding the adverse effects of long-term exposure to outdoor air pollution on the development of these outcomes in low- and middle-income countries (LMICs).

Objective: To systematically evaluate the epidemiological evidence regarding the associations between long-term exposure to outdoor air pollution and respiratory symptoms in LMICs.

Methods: We searched for literature up to September 2022 in Embase (Ovid), Medline (Ovid), and Web of Science (Core Collection). The air and gaseous pollutants studied included particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2), and black carbon (BC), and exposure was 1-year duration or more. We conducted a systematic review and meta-analysis with a random-effects model to calculate the relative risk (RR) estimates. The study protocol was registered in advance in **PROSPERO - CRD42022311326**.

Results: Of the 1246 studies identified, only six met our inclusion criteria, and these six reported $PM_{2.5}$, PM_{10}, and NO_2 with asthma as the main outcome. Three of these included studies were further included in the meta-analysis because they had data on the same exposure and outcome ($PM_{2.5}$ and asthma). The main result of our study showed a borderline significant association between a 10 $\mu g/m^3$ increase in exposure to $PM_{2.5}$ and an increased risk of asthma (RR 1.21, 95% CI 0.96, 1.50). There was evidence of considerable heterogeneity (I^2 =75.87%). The regression-based Egger test for small-study effects showed no significant publication bias among these three studies.

Conclusion: Long-term exposure to $PM_{2.5}$ seems to increase the risk of asthma in LMICs, but studies are scarce and there is a large need for more research in LMICs in this field.

Keywords: Air pollution, asthma, respiratory symptoms, LMICs, long-term, respiratory diseases

Introduction

In low-, middle-, and high-income countries, outdoor air pollution is one of the biggest health and environmental problems (1, 2). Over the previous years, these problems have become worse, especially for low- and middle-income countries (LMICs) because of rapid industrialization and urbanization, population growth, and changes in the rates of non-communicable diseases (2, 3, 4). Air pollution is described as the presence of substances in the air that are detrimental to humans and are linked to an increased risk for premature deaths resulting from lung cancer, chronic obstructive pulmonary disease (COPD), lower respiratory infections, and cardiovascular diseases (5, 6). Air pollution emanates from both natural sources (dust, pollen, mold spores) and anthropogenic activities (man-made activities such as industrial processes, construction work, combustion of fossil fuel, cigarette smoking, wood stove burning, and road traffic) (5, 7, 8).

Most of the world's population presently lives in countries where the levels of air pollution according to the World Health Organization (WHO) air quality guidelines are significantly exceeded due to emissions from anthropogenic activities (9). Although the air quality in high-income countries (HICs) has tremendously improved since the 1970s, the harmful health effects of air pollution exposure still remain, and they are posing an even bigger health threat in LMICs where pollution levels are higher (10). Populations of Sub-Saharan Africa, and Central and Southern Asia continue to experience exposure to high levels of air pollution (11). Simultaneously, there is a lack of sufficient data on the magnitude of the health impacts of outdoor air pollution in most parts of the African continent (12, 13).

In the last years, air pollution contributed to 11.5% of deaths around the world (6). According to the Global Burden of Disease (GBD) 2019 Study, outdoor air pollution has been acknowledged as a risk factor for many of the world's dominant causes of death, such as lung cancer, respiratory diseases e. g. asthma, stroke, and heart disease (2, 6). The GBD 2019 study further pointed out that approximately 4.51 million premature deaths occurred globally in the recent year due to outdoor air pollution (2).

There is growing evidence in relation to the adverse health effects of high levels of long-term air pollution exposure, especially on asthma and respiratory symptoms (14, 15). Recent findings from cohort studies have reported that long-term air pollution exposure could cause new asthma development in addition to asthma exacerbations and could cause a delay in lung development (3). Asthma is a chronic respiratory disease that affects people of all ages around the world (16). Asthma is a chronic inflammatory disorder that is characterized by airway hyperresponsiveness, chronic airway inflammation, and airway obstruction causing common symptoms such as wheezing, dyspnoea, cough, chest tightness, and shortness of breath (5, 7, 17, 18, 19). Since the 1960s, the global prevalence, economic burden, mortality, and morbidity from asthma especially in children have been on a swift rise. Even though asthma is most common in developed countries, it is becoming more prevalent in developing countries which is probably due to rapid urbanization (20). Globally, about 300 million people around the world presently have asthma (21), with around 50% increase in prevalence every decade (20). Phase I of the Global Asthma Network (GAN) evaluated the global prevalence of present asthma symptoms in children, adolescents, and adults to be 9.1%, 11.0%, and 6.6%, respectively (22). In 2019, the GBD predicted 21.6 million disability-adjusted years (DALYs) ascribed to asthma across all ages worldwide. Among the dominant causes of burden of disease, asthma was rated 34th, which was responsible for a 5th out of the total DALYs from chronic respiratory diseases (22).

Although both the burdens of air pollution and asthma morbidity are major problems in LMICs, there is a lack of systematic overviews from LMICs. To the best of our knowledge, quite a small number of studies have carried out systematic reviews in the field of exposure to outdoor air pollution in LMICs, and no systematic reviews have focused on air pollution in relation to asthma and respiratory symptoms in adults in this area. Such overviews can be important tools in improving public heath by serving as a base for informed policymaking, arousing public health authorities and institutions to invest in more effective measures to cause a decline in exposure to air pollutants, and pinpointing out knowledge gaps where more original research studies are needed. Thus, the main aim of this systematic review is to investigate the association between long-term health effects of outdoor air pollution and asthma and respiratory symptoms among adults in LMICs.

Research Question

Does long-term exposure to air pollution increase the risk of asthma and respiratory symptoms among adults in LMICs as compared to adults with relatively low levels of exposure to air pollution?

Methods

Design

This systematic review and meta-analysis was conducted according to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (23). The completed PRISMA checklist can be found in Appendix Table D. The study protocol was registered in advance in International Prospective Register of Systematic Reviews (PROSPERO-CRD42022311326). We used the World Bank’s classification of the low-and middle-income countries (24).

Eligibility criteria

The inclusion and exclusion criteria are explicitly described in **Box 1**.

Inclusion criteria

Types of participants/population, study period, and study setting: Studies conducted on human adult populations exposed to outdoor air or gaseous pollutants of ≥ 1 year up to September 2022 in low- and middle-income countries (LMICs- as defined by the World Bank Classification.

Exposure: Studies that reported on exposure to either of the following outdoor air or gaseous pollutants: particulate matter <2.5 µm in aerodynamic diameter ($PM_{2.5}$), <10 µm in aerodynamic diameter (PM_{10}), nitrogen dioxide (NO_2), and black carbon (BC).

Comparison: Cohort studies that reported on exposure to lower levels of air or gaseous pollutants in the same population.

Outcomes: Asthma, wheezing, cough, and dyspnea

Study designs: Cohort studies, and cross-sectional studies with registered air pollution exposure >1 year back in time, and with the following effect estimates: odds ratio (OR), relative risk (RR), and hazard ratio (HR).

Exclusion criteria

- Non-availability of full texts
- Non-English studies
- Children
- Qualitative studies, and studies that are not original research papers.

Box 1. Inclusion and exclusion criteria

Search strategy

The search strategy was developed in collaboration with a librarian at the medical faculty, University of Bergen. The search strategy for all databases, the interface through which the database was searched, and the dates of coverage are attached as Appendix Table A. We searched systematically in Embase (Ovid), Medline (Ovid), and Web of Science (Core Collection) up to September 20th, 2022.

Data management and screening

All identified studies were exported to EndNote 20 from the three databases and duplicates were removed first in EndNote 20 and then in Rayyan, a web-based research collaboration platform, was used for screening (25). Reviewers AA and SX independently screened titles and abstracts of all records retrieved from the database searches according to the inclusion criteria described above, after which the full texts of possible eligible studies were obtained. AA and SX proceeded to screen all the included full text studies. Disagreements on which studies to include for full text screening were resolved by AJ in dialogue with AA and SX.

Data extraction

AA and SX independently extracted data from the included studies using a standardized pre-piloted data extraction form in an Excel sheet. See Appendix Table E. The form was adapted from The Cochrane Collaboration (26) and modified to suit the data extraction of the included studies of this review. Extracted data included year of publication, study locations, study designs, duration of follow-up, pollutants studied, outcomes reported, and effect estimates.

Quality assessment

The quality of included studies was independently scored by two reviewers (AA and SX) and any disagreement was resolved by AJ. Quality was assessed using the Risk of Bias In Non-randomized

Studies-of Exposure (ROBINS-E) tool developed by the ROBINS-E Development Group led by Higgins and co-workers (27), but we adopted the format of the ROBINS-E form by Park and co-workers from their supplementary data (28). This tool provides an orderly way to assess the risk of bias in observational epidemiological studies. It includes seven domains of bias: confounding, exposure classification, participant selection, departure from intended exposure, missing data, and outcome measurement. Each domain is addressed using a series of signaling questions with the purpose of collecting significant information on the study and analysis being evaluated (27). In addition, three judgements are made after the important signaling questions have been answered, then, an overall judgement is carried out for each of these considerations (27).

Meta-analysis

A meta-analysis was performed where two or more studies were identified for the same pollutant and the same health outcome. In view of the anticipated variations in both population sizes and pollutants, we *a priori* resolved to pool estimates using DerSimonian and Laird random-effect meta-analysis (29).

In the case when a study reported OR estimates for an increment different than per 10 μg/m^3 (30), we converted the estimate to per 10 μg/m^3 by calculating slope (Beta) and standard error (SE) per 1 μg/m^3, multiplied by 10 and then exponentiated. We adopted the standard equations below from Chen et al., (31)

Beta = LN (RRo) /increment

SE = (LN(RRo_high) — LN (RRo_low)) / (2 ×1.96 x increment)

RRc = EXP (Beta × 10)

RRc_low = EXP (Beta × 10 — 1.96 × SE × 10)

RRc_high = EXP (Beta × 10 + 1.96 × SE × 10)

RRc is the estimate we converted to, and RRo is the effect estimate originally reported in the paper with its low (RRo_low) and high (RRo_high) end of the confidence interval (CI).

Statistical investigation of heterogeneity of effect estimates between studies were evaluated using tau2, shown in the form of an 80% prediction interval around the mean effect (32), Q-test (chi^2), and I^2 index. If the *P* values were below 0.10 in the Q-test and/or the I^2 index was higher than 75%, then the pooled analysis was considered significantly heterogeneous (28). To estimate the possible publication bias, we conducted Egger's weighted linear regression (33). All statistical tests and plots were done on STATA version 17.0 statistical software.

Certainty of evidence assessment

For each pollutant exposure and outcome, the certainty of evidence (CoE) was judged by adapting the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach developed by a group of experts convened by the WHO (34, 35, 36). The GRADE domains consist of five domain downgrade reasons: limitations in studies, indirectness, inconsistency, imprecision, and publication bias and three domains of upgrade reasons: large effect size, confounding domain, and concentration-response gradient domain. In a nutshell, we began the rating steps at moderate certainty of evidence due to the risk of unmeasured confounding in observational studies. Thereafter, we downgraded or upgraded the CoE according to the five (downgraded domains reasons) and the three (upgraded domains reasons) respectively.

Results

Included studies

Our detailed literature search across Embase, Medline, and Web of Science identified 1,246 studies as shown in **Figure 1**. Following the removal of duplicates from the records exported to Rayyan software from EndNote, 16 records were further removed as duplicates in Rayyan, after which we screened the titles and abstracts of 738 studies. 721 studies were excluded because of the following reasons: wrong population (n=305), wrong study design (n=152), wrong outcome (n=97), wrong exposure (n=50), not related to the topic of interest (n=33), wrong publication type (n=20), indoor exposure (n=23), occupational exposure (n=14), studies not in LMICs (n=12), short-term study (n=13), animal studies (n=2). Only 17 studies were eligible for an in-depth full text screening. However, just 6 of these studies (30, 37, 38, 39, 40, 41) met our inclusion criteria while 11 studies were excluded. Of these 11, 5 studies did not report on outcome of interest, 3 studies did not report on any of the pollutants of interest, 2 studies had the wrong study design and 1 study reported on short-term exposure. From the 6 included studies, 3 studies were included in the meta-analysis, while 3 studies did not provide estimates suitable for our meta-analysis and were included only in the descriptive part of this review.

Study characteristics

Of the six included studies, one study recruited participants 15 years old and above, and considered them as adults (40). For the other five studies, the study participants were ≥ 18 years old. The outcomes reported were wheeze (2), cough (3), dyspnoea (2), and asthma (3). Studies were carried out in six different LMICs. Four studies were carried out in India, one in South Africa, and one was a multi-country study including participants from India, South Africa, China, Russia, Ghana, and Mexico. These studies were published between 2001 and 2022, and the duration of studies ranged from one year to ten years. The sample size of participants ranged from 572 to 39,054. The study designs used were 1 cohort study, and 5 cross-sectional studies but with pollution exposures measured back in time. A general description of each included study is shown in **Table 1** and Appendix Table C.

Yan et al., (37) reported both hazard ratio (HR) and odds ratio (OR) as their effect estimates. The pooled HR was the main effect estimate reported in their article while the pooled OR was reported as part of the supplementary data. To be able to include this study in our meta-analysis, we chose the pooled OR from the Yan study.

Our review found only two studies from the African continent by Bagula et al., (30) and Ai et al., (38) that reported on the exposure to $PM_{2.5}$ and NO_2 in South Africa and $PM_{2.5}$ in Ghana and South Africa respectively.

Summary of Findings of the included studies

From the most recently published paper in our included study by Yan et al., (37), it was observed that after adjusting for cities (Model 4 as described in **Table 2**), there was no significant association between $PM_{2.5}$ and asthma. These differences in the results between Model 4 and the other models can be attributed to the diverse economic and medical conditions that can be seen in the four different cities (Rizhao, Shenyang, Taiyuan, and Tianjin), but they can also be due to different pollution levels in the different cities. From the study by Yan et al., we included OR without adjusting for cities in the meta-analysis. This information was retrieved from the 'Table S8 of the Supplementary materials' and showed a significant association between 10µm/m^3 increase of $PM_{2.5}$ and asthma.

In the study by Yan et al., high-resolution $PM_{2.5}$ concentration estimates of 1 km x 1 km was used because it provided more accurate exposure gradients within population clusters. Moreover, this was a large cohort study in Northern China with an almost 10-year follow-up to define the concentration-response (C-R) curves between prolonged outdoor exposure to $PM_{2.5}$ and the onset of chronic respiratory diseases. It is also the first of its kind to consider passive smoking status as an adjustment variable because second-hand smoke is a significant risk factor of respiratory diseases in never smokers. Another important strength of this study was that the authors carried out bi-pollutant models such as $PM_{2.5}$-NO_2 and $PM_{2.5}$-SO_2 to assess the impacts of multi-pollutant exposure on chronic respiratory outcomes. On the other hand, recall bias for specific self-reported contents such as lifestyle factors was experienced due to the retrospective cohort study design. The study also lacked time-scale data on lifestyles such as smoking and drinking status, hence they were not analysed as time-varying covariates. (37).

From the cross-sectional study carried out among adults from four informal settlements in the Western Cape province of South Africa by Bagula et al., (30), participants from Khayelitsha had the highest proportion of wheezing (13.4%), shortness of breath (10.5%), and chest tightness (12.2%) in the last 12 months. For shortness of breath after exercise, Masiphumelele (Noordhoek) had the highest proportion with 25.9%, while Oudtshoorn had the highest proportion of participants bringing up phlegm from the chest during winter with 12.2%. A major strength of this study was the use of Land-Use Regression models which was the first to be used in Africa to evaluate annual exposure to outdoor air pollution and to assess its link with cardiorespiratory outcomes. Thus, these models were used to assess each participant's annual concentration of exposure to NO_2 and $PM_{2.5}$ at their present residential address during the study duration.

Generalizability of their findings may not be possible neither to the men nor the general population because most of the participants (about 88.5%) were women (30).

The study by Ai et al., (38) showed that men and smokers had higher risk of asthma than women and non-smoker, respectively. Almost 12% of the asthma cases in men were attributable to $PM_{2.5}$. One significant strength of this study was this estimation of attributable burden which pointed out the public health benefit that would be accomplished if relevant interventions are put in place to reduce the exposure to air pollution. But some weaknesses were also identified. This study employed a cross-sectional study design which was not able to determine the causal relationship between $PM_{2.5}$ and asthma. The authors could not control for potential confounders because of lack of information of the residential changes of the participants which may also have an impact on the exposure assessment. If a person lived somewhere with high pollution exposure at the time of the exposure measurement and then moved to a place with low pollution exposure, he would in fact have a lower pollution exposure on average than what was registered in the study. The opposite could also happen for some participants. This could lead to underestimation and overestimation of the effects, respectively.

Khafaie et al., (39) conducted the first study among diabetic and non-diabetic participants in India that investigated the long-term effect of background concentration of air pollution on the respiratory health. The findings from this study showed that living in a region with high air pollution concentration is linked with chronic respiratory problems. This study has followed quality controlled standard protocols. Nonetheless, a major weakness in this study was the presence of residual confounding even though the authors adjusted for known and possible confounders. These residual confounders could be since the non-diabetic participants were selected from the hospital staff. It is likely that this group of participants more often live in the city centre which has higher levels of air pollution, and they were younger and so they could likely spend considerable amount of their time outdoors (39).

The study by Kumar et al., (40) was one of the few studies carried out in a developing country to use an ecological method to conduct a comparison between the respiratory health status of residents of an industrial town with a high level of air pollution and residents of a town with lower air pollution. A major strength of this study was a very high participation rate (90%), and data was collected from each town at the same time and from the same field investigators. Also, calibration of the instruments was regularly done against a standard. However, the possibility to carry out individual air sampling and to quantify the effect of various levels of air pollutants was not available, instead every person living in the same study region was defined with the same level of air pollution exposure (40).

Findings from Chhabra et al., (41) indicated a significantly higher ratio of symptomatic persons in the higher age groups both in the lower-and higher-pollution zones. Also, a highly significant linear relationship exists between increasing age and occurrence of symptoms. It was further shown that increasing age, smoking, male sex, and lower socioeconomic status were strong independent risk factors for the occurrence of chronic respiratory symptoms, cough, and dyspnoea. However, wheezing showed no consistent pattern in relation to its association with air pollution.

Meta-analysis findings

From the six included studies, we conducted meta-analysis on three of these studies because they reported on the same $PM_{2.5}$ exposure and the same asthma outcome with effect estimate of OR or comparable (30, 37, 38). All effect estimates were >1. However, the smallest study (30) had a very wide confidence interval, and the pooled estimate was borderline significant with RR 1.21 (95% CI 0.93, 1.50) as shown in **Figure 2.** There was evidence of considerable heterogeneity (I^2

=75.87%). The regression-based Egger test for small-study effects showed no significant publication bias among these three studies.

Risk of bias assessment in individual studies

According to our risk of bias assessment, most of the included studies *(30, 37, 38, 40, 41)* were moderate while only one study by *(39)* was rated high (**Figure 3**) . The detailed analysis based on ROBINS-E domains is summarized in **Table 1** and Appendix Table B.

Certainty of evidence

Table 3 gives a description of the application of the GRADE tool to the body of evidence for $PM_{2.5}$ and asthma and the rationale for the rating of the various GRADE domains. We concluded a downgrade with one level for both inconsistency and imprecision because there was considerable heterogeneity (I^2 = 75.87%) and sample size was met but the confidence intervals were wide and included 1. On the other hand, an upgrade with one level was concluded for the concentration-response gradient because two studies reported plausible shape of the concentration-response gradient. In sum, we rated the overall GRADE assessment for our included studies to be low.

Discussion

This current systematic review and meta-analysis showed that exposure to $PM_{2.5}$ increased the risk of asthma. Studies that were not included in the meta-analysis but were included in the narrative part of this review further indicated a significant impact of PM_{10} on the development of respiratory symptoms such as cough and dyspnoea. Only one study (30) included in this review reported on NO_2, it showed no significant association between NO_2 and respiratory symptoms.

Although this present review included only six studies and conducted meta-analysis on only three of these, we found that certain factors contribute greatly to vulnerability to the adverse effects of air pollution. Geography, economic conditions, sex, and age were all of importance. Geography can play a direct part with different areas having different levels of air pollution exposure. For example, Bagula et al., (30) found that participants from Khayelitsha had higher proportion of asthma and respiratory outcomes than participants from the other locations in the study, possibly because they were also exposed to the highest levels of NO_2 and $PM_{2.5}$ as indicated by the annual mean concentrations. However, geography can also affect the vulnerability to adverse health effects of air pollution, regardless of the air pollution levels. The same levels of PM exposures may have different health effects in urban and rural areas because the components of PM vary in different locations (42). Another example is that warmer geographic areas have more pollen than colder areas, and pollen may interact with other outdoor air pollution causing increased vulnerability to pollution health effects in a population (43). Economic conditions are also of relevance. The associations between air pollution and asthma in poorer cities or neighborhoods are stronger than in wealthier areas (44, 45). The findings by Ai et al., (38) in addition showed that sex is another factor. It was shown that males had higher risk of asthma due to the exposure to $PM_{2.5}$ (RR 1.09, 95% CI 1.04, 1.14) than females (RR 1.01, 95% CI 0.97, 1.06). This is also consistent with the previous studies of Alhanti et al., (46). An underlying reason to this higher association among the males might be that men are prone to engage in outdoor activities than women, hence causing exposure to higher levels of pollution and then inducing the likelihood of asthma occurrence. In a cohort study from Northern China conducted by Yan et al., (37) one of the included studies in this review, it was noted that participants younger than 60 years had more asthma due to exposure to outdoor $PM_{2.5}$ air pollution than the younger participants. The reason for higher potential vulnerability to air pollution effects in younger people may be linked to younger people staying outdoors more. However, sufficient data on the elderly on the impact of $PM_{2.5}$ is lacking, hence Fan et al., (47) recommended that more studies are needed to focus on the elderly since they are more prone than the younger populations to various chronic diseases and reduced immune function.

WHO has developed guidelines on recommended limit levels of outdoor air pollution which are largely adopted as a reference guide by policymakers globally to set standards and goals for the management of air quality. These guidelines give evidenced, health-based standards for air or gaseous pollutants that cities should employ as their air quality targets (48). The updated WHO 2021 guidelines recommend annual average concentration of 5μg/m^3, 15 μg/m^3 and 10 μg/m^3 for $PM_{2.5}$, PM_{10} and NO_2 , respectively (48). In our six included studies, the WHO recommended guidelines on the annual mean concentrations were exceeded. Yan et al., (37) reported the average concentration of annual mean of $PM_{2.5}$ exposure from 2000 to 2009 of the four cities in their cohort study was 66.5 μg/m^3. Rizhao had the lowest level of annual concentration of 41.4 μg/m^3 while Tianjin had the highest level of annual concentration of 96.7 μg/m^3. Ai and co-workers reported the annual average $PM_{2.5}$ concentration of India 49.7 μg/m^3 and China had 47.0 μg/m^3. Kumar and co-workers reported the levels of PM_{10} and NO_2 in India were 112.8 μg/m^3 and 27.4 μg/m^3, respectively. Chhabra et al., (41) reported the levels of NO_2 in the lower-pollution and higher-pollution zones were 28.6 ± 9.3 μg/m^3 and 49.0 ± 31.0 μg/m^3, respectively. Khafaie et al., (39) also reported the annual average concentration of PM_{10} at the participants 'residence to be 300.48 ± 98.3 μg/m^3. These findings are in agreement with the report from the development aid (49) that South and East Asian cities emerge as the most polluted cities globally. It was further reported by Ai et al., (38) that the average $PM_{2.5}$ concentration in Ghana and South Africa were 29.0 μg/m^3 and 16.9 μg/m^3 which also exceeded the WHO recommended guidelines. From a cross-sectional study of four study areas in South Africa by Bagula and co-workers (30), the estimated annual concentration of NO_2 was 16.9 μg/m^3, and the estimated annual $PM_{2.5}$ concentration was 10.1 μg/m^3.

Findings from meta-analysis

The main result of our study showed a borderline significant association between 10 μg/m^3 increase in exposure to $PM_{2.5}$ and increased risk of asthma (RR 1.21, 95% CI 0.96, 1.50). In the meta-analysis, however, we observed a considerable heterogeneity between studies (I^2 =75.87%). This is to be expected given the differences in methodology, exposure information source, concentration, geographical location, and duration as shown in Table 1 and Appendix Table C. In addition, composition of PM and study population characteristics are also likely to differ between studies, causing increased heterogeneity. The composition of $PM_{2.5}$ across studies will vary in different locations due to different industries and sources of emissions.

These factors aforementioned are also emphasized in the systematic reviews and meta-analyses conducted by Chen et al., (31), Park et al., (28), Badida et al., (50) and Rajak et al., (51). It would be valuable to investigate properly the sources of heterogeneity in our review, but unfortunately, we could not carry out subgroup analyses due to the low number of studies (n=3) included in our meta-analysis.

This review did not focus on the duration of exposure to the air pollutants and the effect of duration on exposure-outcome associations. This is because the duration of exposure reported in each of the included studies varied. It is important to note that these results were based on the current availability of observational studies with both short and long follow-up periods between one to ten years, and this may have impacted the results of our meta-analysis. The duration will to some extent be linked with the effect size because the longer the duration, the more likely it is that the risk will increase. For instance, the study of Yan showed the longest follow up (almost 10 years) and had the highest effect size (OR 1.36 95% CI: 1.15, 1.60). The other two included studies by Bagula and Ai had shorter follow up duration of one and three years, respectively with effect sizes of OR 1.27 95% CI: 0.95, 1.71 and RR 1.05 95% CI: 1.01, 1.08.

Comparison with other studies from LMICs

No other meta-analysis exists on air pollution and asthma and respiratory symptoms in LMICs, but some meta-analyses from LMICs are published on other respiratory outcomes. Dimala et al., (52) reported that a significant association exist between exposure to $PM_{2.5}$, and PM_{10} and the incidence of pulmonary tuberculosis [$PM_{2.5}$ (pooled aRR 1.12, 95% CI 1.06, 1.19, n = 6); PM_{10} (pooled aRR 1.06, 95% CI 1.01, 1.12, n = 8).

In a systematic review and meta-analysis by Park et al., (28), results showed that $PM_{2.5}$ is associated with increased incidence of chronic obstructive pulmonary disease (COPD) (pooled hazard ratio (HR) pr 10 $\mu g/m^3$ increase 1.18, 95% CI 1.13, 1.23). It was also noted that NO_2 is marginally associated with increased incidence of COPD (pooled HR pr 10 $\mu g/m^3$ increase 1.07, 95% CI 1.00, 1.16). PM_{10} on the other hand seems to have no significant impact on the incidence of COPD (pooled HR pr 10 μg/m^3 increase 0.95, 95% CI 0.83, 1.08). The findings from these mentioned reviews corroborate with the findings of our review that long-term exposure to air pollution has a significant association with health outcomes.

The underlying reason why $PM_{2.5}$, PM_{10}, and NO_2 are largely associated with diseases of the respiratory system is through irritation of the respiratory system (53, 54, 55). Feng et al., (56) has pointed out that inflammation is one of the major mechanisms of the severe health effects of $PM_{2.5}$. Positive findings with $PM_{2.5}$ and PM_{10} in our narrative review are in line with this, however no associations with NO_2 were observed in the papers we examined.

The lack of association between NO_2 and asthma in our review is surprising, but only one study included NO_2, and this study had a small study population. So, the lack of association is probably due to the small study population and does not necessarily mean that NO_2 is not harmful in LMICs. A higher number of studies for inclusion in our review would probably alter this lack of association.

Comparison with studies from high-income countries (HICs)

Findings from a nationwide cohort of 50,884 U.S women by Young et al., (57) on ambient air pollution exposure and incident adult asthma showed that greater $PM_{2.5}$ concentrations were associated with incident wheeze and asthma. For an interquartile range (IQR) difference (3.6 μg/m^3) in estimated $PM_{2.5}$ exposure, the adjusted odds ratio (aOR) was 1.20 (95% CI 0.99, 1.46) for incident asthma and 1.14 (95% CI 1.04, 1.26) for incident wheeze. For NO_2, there was evident association with incident wheeze [aOR pr IQR difference 11.9 μg/m^3) 1.08, 95% CI 1.00, 1.17]. Neither pollutant was significantly associated with incident cough ($PM_{2.5}$: aOR = 0.95, 95% CI 0.88, 1.03; NO_2: aOR = 1.00, 95% CI 0.93, 1.07). With our current study showing a borderline significant association between exposure to $PM_{2.5}$ [RR pr 10 μg/m^3 increase 1.21 (95% CI 0.96, 1.46)] and the risk of asthma, we can compare the findings and conclude that exposure to $PM_{2.5}$ seems to have a harmful impact on the risk of asthma among adults.

In the Weichenthal et al., (58) large population-based cohort study of about 1.1 million adults in Toronto, Canada, they found no clear evidence of positive associations between ambient ultrafine particles and respiratory disease incidence. However, per IQR increase in ambient $PM_{2.5}$ and NO_2 were associated with increased risk of COPD, and adult-onset asthma. For $PM_{2.5}$: COPD; [HR 1.07 (95% CI 1.06, 1.09)]; adult-onset asthma [HR 1.01 (95% CI 1.00, 1.02)]; For NO_2: COPD [HR 1.10 (95% CI 1.09, 1.11)]; adult-onset asthma [HR 1.04 (95% CI 1.03, 1.05)]. Hence, a line of comparability is also observed between the study by Weichenthal (58) and our present review that outdoor $PM_{2.5}$ pollution exposure increases the risk for asthma.

In agreement with this present review is also the findings by Liu et al., (59) from the Danish Nurse Cohort of 28,731 female nurses. The authors found positive associations between long-term exposure to outdoor air pollution for $PM_{2.5}$ [HR 1.29 per IQR (95% CI 1.03, 1.61)] and NO_2 [HR 1.16 per IQR (95% CI 1.07, 1.27)] and asthma incidence. A non-significant association for asthma with PM_{10} (adjusted OR 1.04; 95% CI 0.88, 1.23 per 10 $\mu g/m^3$) and $PM_{2.5}$ (adjusted OR = 1.04; 95% CI: 0.88, 1.23 per 5 $\mu g/m^3$) were found in the European Study of Cohorts for Air Pollution Effects (ESCAPE) study by Jacquemin et al., (60), and a borderline significant association for NO_2 (adjusted OR 1.10; 95% CI: 0.99, 1.21 per 10 $\mu g/m^3$). Fisher and co-workers (61) in their studies among the American Nurses' Health Study of 121,701 female nurses found no associations between exposures to $PM_{2.5}$, PM_{10}, and asthma incidence (adjusted HR 0.90; 95% CI 0.73, 1.12 per 10 $\mu g/m^3$ and adjusted HR 0.94; 95% CI 0.84, 1.06 per 10 $\mu g/m^3$), respectively).

Certainty of evidence

We applied an adopted GRADE approach to evaluate certainty in the epidemiological body of evidence. Overall, $PM_{2.5}$ showed more consistent association with asthma and respiratory symptoms than PM_{10}. A reasonable explanation for this difference might be because there are fewer studies of PM_{10} relative to $PM_{2.5}$ (31) and because $PM_{2.5}$ enters deeper into the airways. There is more complexity in the application of the risk of bias than in using a simple checklist because careful interpretations to make appropriate judgement are needed.

Strengths and limitations

One of the strengths of our review is the collective and independent efforts of the collaborative team made in the conduct of the systematic review to ensure validity. This process helped to avoid subjective bias in the article inclusion process.

Another strength worthy of note is the professional involvement of the librarian from the medical faculty at the university in the search of the relevant databases and the development of the search terms. This involvement helped this review to identify the relevant databases and to perform broad literature searches across these databases and avoided unnecessary duplicates of articles.

Also, the performance of a pilot search improved the credibility, relevance, and methodology of the review. Correcting the errors in the pilot search ensured a robust high-quality search in the work with the main review.

The reviewers of this study did a thorough review of all the included studies by reading through also the supplementary materials associated with the selected papers. This helped us to extract valuable additional information such as identifying from the paper by Yan et al., (37) that the effect estimates of our interest was not reported in the main paper but in the online supplement.

Lastly, we ensured that the effect estimates dealt with comparable exposure increments. Two of the included papers reported on 10 μg/m^3 increment while one paper looked at IQR with the IQR in that study being 5.12 μg/m^3. We converted the OR for increment less than per 10 μg/m^3, that is, per interquartile range increase (IQR) of 5.12 μg/m^3 in $PM_{2.5}$ in one of the included studies to OR per 10 μg/m^3 increase in exposure to $PM_{2.5}$. The conversion formula is reported in the 'Methods section'. Because of this conversion, we were able to conduct more direct comparisons of the effect estimates.

When interpreting the results from this review, certain limitations should be noted. A significant limitation of our meta-analysis is that the small number of included studies affected heterogeneity. To be included in a meta-analysis, different studies should report the same kind of effect estimate, in addition to having comparable exposures and outcomes. In our meta-analysis, two of the included effects estimates were odds ratios and one was relative risk. We initially wanted to streamline the effect estimates by converting the RR to OR, However, such conversion was not possible because the exposure variable was a continuous variable, and we could not identify formulars for the conversion of confidence intervals for estimates based on continuous exposure variables. Hence, we adopted the recommendations of (62, 63, 64) that OR and RR can be interpreted interchangeably for rare outcomes when the prevalence of OR is less than 10%. We included both OR and RR in the meta-analysis and interpreted the OR as RR. Although this approach was not optimal, we found it the only way to conduct meta-analysis, since there are extremely few studies of long-term pollution exposure and asthma in LMICs. Since the outcomes were relatively low prevalence 'less than 10%' (62, 63, 64) in our review, interpreting ORs as RRs should not present a major methodological problem. The prevalences of the three studies are 0.2%, 6.6%, and 15.7%, respectively (30, 37, 38). Only three studies out of the six included studies reported the impact of $PM_{2.5}$ and asthma on adults.

Some potential biases were encountered in this review. The health outcomes of interest in this review (asthma, cough, wheeze, and dyspnoea) were mainly based on self-report which might have introduced recall bias as reported by Yan and Bagulas' studies. Coughlin (65) (pg. 87) defined recall bias as "a form of differential misclassification bias and the risk estimate may be biased away from or towards the null". For instance, Yan's study was a retrospective cohort study that might have caused a recall bias for some self-reported details, lifestyle habits such as physical activity etc. So, both under- and over- estimations may have taken place. However, the pollution exposures were measured objectively, and the outcomes were defined by self-report based on current disease and through registry. Also, our search was limited to English, which means we may have missed some studies published in other languages. This could have resulted in biased effect estimates and reduced generalizability. Through an additional search where we also included non-English papers, however, we found that only a limited number of studies were missed in this manner: one study was published in Bulgarian and two studies in Chinese.

It is challenging to assess the impact of long-term exposure of air pollution on human health due to the large amounts of efforts and resources needed to conduct a long-term prospective observational study. To measure and estimate the level of air pollution exposure over expansive areas, special technology is required. The small number of studies found through our literature search mirrors this great challenge in designing such a study to explore the impact of air pollution on lung health in LMICs. This is due to the lack of resources in LMICs. It is easier in the HICs with more research funding possibilities to conduct studies with costly technologies.

Implications of the study

Our findings support that long-term exposure to air pollution is harmful for asthma development in low-and middle-income countries. Most of all, this review has revealed a striking lack of studies in this field in LMICs. There is an acute need for more studies to be conducted.

The considerable heterogeneity observed across included studies implies large variation regarding air pollution and respiratory diseases across LMICs. This should be taken into consideration and studies should be planned for multiple locations such as in Africa, Eastern Mediterranean, and South-East Asia regions where no or few research projects have been carried out. Also, in areas where there is significant contribution of dust to the $PM_{2.5}$ composition, our pooled relative risks (RRs) may not be applicable and the need for separate studies will be even larger.

The current review provides more evidence for why implementation of air quality monitoring should be important for policy makers. The results can also be important for disease prevention: identifying patients at risk and advising them to avoid pollution as much as they can to avoid becoming sick.

Another possible implication is related to costs. If this study can contribute to increased air quality monitoring and knowledge about associations between pollution and respiratory diseases in LMICs, a decrease in health costs could be a significant co-benefit.

As pointed out by Dominski et al., (55) a substantial percentage of the total health expenditure is spent on respiratory diseases. In the Dominski study, average yearly direct costs of 764 USD to 929 USD to cover for medication, transportation, job loss and other expenses. In addition, hospitalizations have been shown to be a major cost-driver of severe asthma for the (66).

The total health cost acquired from air pollution is enormous, and the decrease in associated health costs would be a significant co-benefit of implementation of air pollution preventive measures (67).

Conclusion

Our systematic review and meta-analysis indicate a positive association between long-term exposure to outdoor air pollution ($PM_{2.5}$) and the development of asthma among adults. The findings of this review contribute to scientific evidence and may help underpin targeted mitigation measures to decrease the health burden associated with outdoor air pollution.

The LMICs are experiencing environmental problems especially because of their fast urbanization, and economic transformation, and the problems are further aggravated by poverty. These factors contribute greatly to the increasing levels of outdoor air pollution. Although there is increasing knowledge and epidemiological studies on air pollution in the developed countries, such information is still lacking in the LMICs. We propose that more primary studies are needed to fill these knowledge and methodological gaps and to strengthen the current evidence to inform and support policy makers.

CRediT authorship contribution statement

Achenyo Peace Abbah, Shanshan Xu, Ane Johannessen: Conceptualization, Methodology. **Shanshan Xu, Ane Johannessen:** Supervision. **Achenyo Peace Abbah:** Writing – Original draft. **Achenyo Peace Abbah, Shanshan Xu, Ane Johannessen:** Writing- Review & Editing.

Declaration of interest

The authors declare no competing interests.

Funding source

There was no funding for this study.

Acknowledgements

We would like to acknowledge the contribution of university librarian Elisabeth Ebner for her assistance with the electronic search strategies and suggestions for the relevant databases.

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Tables and Figures

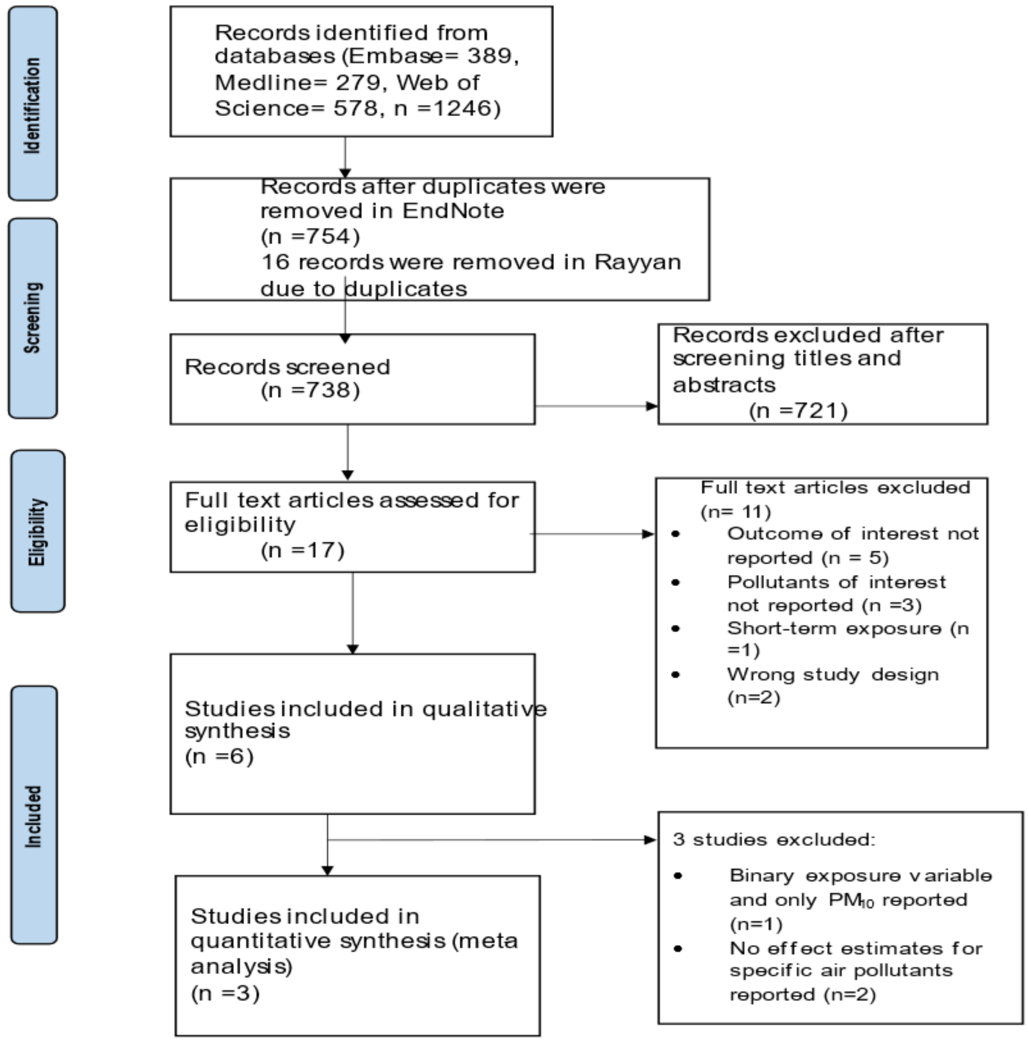

Figure 1. PRISMA flowchart of the study identification and selection process.

Retrieved from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 1. Characteristics of the included studies

Study author	Year of publication	Study location(s)	Study design	Number of participants	Duration (years)	Pollutants studied	Outcomes reported	Effect estimates reported	Risk of Bias using ROBINS-E
Yan et al., (37)	2022	Northern India	Cohort	39,054	9.8	$PM_{2.5}$	Asthma	Odds ratio	Moderate
Bagula et al., (30)	2021	South Africa	Cross-sectional	572	1	$PM_{2.5}$, NO_2	Asthma	Odds ratio	Moderate
Ai et al., (38)	2019	China, India, Ghana, Mexico, South Africa & Russia	Cross-sectional	29,249	3*	$PM_{2.5}$	Asthma	Relative risk**	Moderate
Khafaie et al., (39)	2017	India	Cross-sectional	865	1	PM_{10}	Cough, dyspnoea	Odds ratio	High
Kumar et al., (40)	2004	Northern India	Cross-sectional	3603	2*	PM_{10}, NO_2	Cough, wheeze	Odds ratio	Moderate
Chhabra et. Al, (41)	2001	India	Cross-sectional	4171	10*	NO_2	Wheeze, cough, dyspnoea	Odds ratio	Moderate

*The study duration for these cross-sectional studies is listed as more than one year because the air pollution exposure was measured back in time even though it was a one-study participation.

**Prevalence ratio was assessed which is mathematically identical to relative risk (64), hence this review used the term RR (relative risk).

NO_2: Nitrogen dioxide, PM_{10}: particulate matter < 10 µm, $PM_{2.5}$: particulate matter < 2.5 µm

Table 2. Adjusted OR (95% CI for the incidence of asthma in relation to each 10 μg/m^3 increase in $PM_{2.5}$) in the study by Yan et al., *(37)*

Adjusted baseline variable	**Asthma** **Odds ratio (95% CI)**
Crude model	1.48 (1.27, 1.73)
Model 1	1.45 (1.24, 1.70)
Model 2	1.45 (1.23, 1.70)
Model 3	1.36 (1.15, 1.60)
Model 4	0.76 (0.55, 1.04)

Abbreviations: Model 1: adjusted for gender (male and female), age, and BMI. Model 2: adjusted Model 1 plus educational level, personal income. Model 3: adjusted for Model 2 plus smoking status, passive smoking status, alcohol consumption, physical activity, and family history of asthma. Model 4: adjusted for Model 3 plus the four cohort cities.

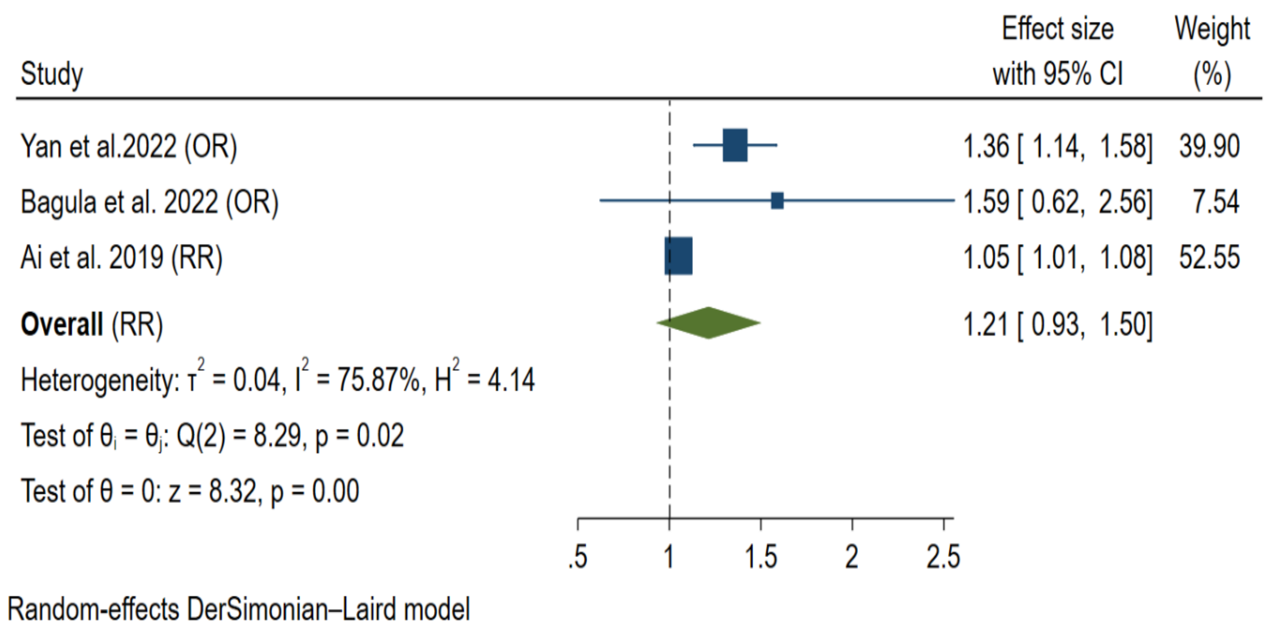

Figure 2. Forest plot of $PM_{2.5}$ and asthma

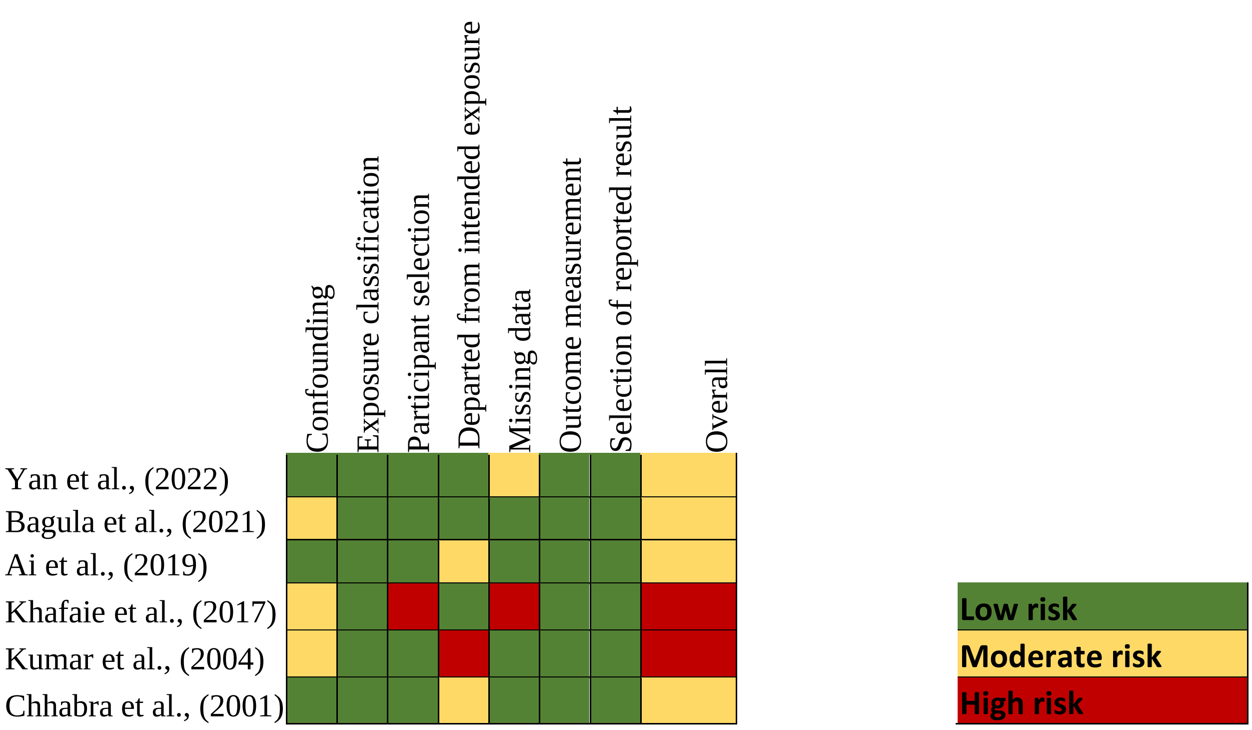

Figure 3. Risk of bias assessment in the included studies

Table 3. Detailed assessment of certainty of evidence for exposure-outcome

	Reasons for downgrade										Reasons for upgrade						Overall
Exposure – Outcome	**A1**	**Rationale**	**A2**	**Rationale**	**A3**	**Rationale**	**A4**	**Rationale**	**A5**	**Rationale**	**B1**	**Rationale**	**B2**	**Rationale**	**B3**	**Rationale**	
$PM_{2.5}$ and Asthma	0	No studies rated high RoB	0	The research question in the studies reflected the PECO question	-1	Considerable heterogeneity (I^2 =75.87%)	-1	Sample size met but confidence intervals were wide and included unity	0	No evidence of publication bias	0		0		+1	Two studies reported plausible shape of concentration-dose gradient	Low

Abbreviations: A1 = limitations in studies (risk of bias); A2 = indirectness; A3 = inconsistency; A4 = imprecision; A5 = publication bias; B1= large effect size (RR); B2 = confounding; B3 = concentration-response gradient.

Appendices

Appendix 1. Search Strategies

Appendix Table A. Search strategies

SEPTEMBER 23, 2022

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to September 22, 2022>

1 Air Pollution/

2 vehicle emission/

3 exp Air Pollutants/

4 traffic-related pollution/

5 Nitrogen Dioxide/

6 Particulate matter/

7 ("air quality" or "air toxic*" or (Air and (pollut* or emission* or exhaust or particulate or particle or "black carbon" or "nitrous oxide" or "oxides of nitrogen" or "nitrogen dioxide" or "NO2" or smoke or "wood burn*" or "wood heat*" or fire-place or fireplace or chimney or stack or "tunnel" or "PM10" or "PM2.5"))).ti,ab,kw.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 (ambient or outdoor*).ti,ab,kw.

10 8 and 9

11 Asthma/

12 respiratory sounds/

13 (Asthma* or dyspnoea* or dyspnea* or cough* or wheez*).ti,ab,kw.

14 11 or 12 or 13

15 10 and 14

16 (afghanistan* or albania* or algeria* or american samoa* or angola* or argentina* or armenia* or azerbaijan* or bangladesh* or belize* or benin* or bhutan* or bolivia* or "bosnia and herzegovina" or brazil* or bulgaria* or burkina faso* or burundi* or cabo verde* or cambodia* or cameroon* or central african republic* or chad* or china* or colombia* or comoros* or democratic republic congo* or congo republic* or costa rica* or "cote d'ivoire" or cuba* or djibouti* or dominica* or dominican republic* or ecuador* or egypt* or united arab republic* or el salvador* or equatorial guinea* or eritrea* or eswatini* or ethiopia* or fiji* or gabon* or gambia * or "georgia republic" or ghana* or grenada* or guatemala* or guinea* or guinea bissau* or guyana* or haiti* or honduras* or india* or indonesia* or iraq* or jamaica* or jordan* or kazakhstan* or kenya* or "democratic people's republic of korea" or kosovo* or kyrgyz republic* or lao pdr* or lebanon* or lesotho* or liberia* or libya* or madagascar* or malawi* or maldives* or mali* or marshall islands* or mauritania* or mauritius* or mexico* or micronesia fed sts* or mongolia* or montenegro* or morocco* or mozambique* or myanmar* or namibia* or nepal* or nicaragua* or niger* or nigeria* or north macedonia* or pakistan* or panama* or papua new guinea* or paraguay* or peru* or philippines* or romania* or russian federation* or rwanda* or samoa* or "sao tome and principe" or senegal* or serbia* or sierra leone* or solomon islands* or somalia* or south africa* or south sudan* or sri lanka* or "st. lucia" or "st vincent and the grenadines" or sudan* or suriname* or syrian arab republic* or tajikistan* or tanzania* or thailand* or timor leste* or togo* or tonga* or tunisia* or turkey* or turkmenistan* or tuvalu* or uganda* or ukraine* or uzbekistan* or uzbek* or vanuatu* or vietnam* or "west bank and gaza" or yemen rep* or zambia* or zimbabwe*).ti,ab,sh,kf.

17 15 and 16

18 limit 17 to english

SEPTEMBER 23, 2022

Embase (Ovid SP) <1974 to 2022 September 22>

1 Air Pollution/

2 Vehicle emission/

3 exhaust gas/

4 exp Air Pollutants/

5 traffic-related pollution/

6 traffic pollution/

7 Nitrogen Dioxide/

8 Particulate matter/

9 ("air quality" or "air toxic*" or (Air and (pollut* or emission* or exhaust or particulate or particle or "black carbon" or "nitrous oxide" or "oxides of nitrogen" or "nitrogen dioxide" or "NO2" or smoke or "wood burn*" or "wood heat*" or fire-place or fireplace or chimney or stack or "tunnel" or "PM10" or "PM2.5"))).ti,ab,kw.

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11 (ambient or outdoor*).ti,ab,kw.

12 10 and 11

13 Asthma/

14 respiratory sounds/

15 (Asthma* or dyspnoea* or dyspnea* or cough* or wheez*).ti,ab,kw.

16 13 or 14 or 15

17 12 and 16

18 (afghanistan* or albania* or algeria* or american samoa* or angola* or argentina* or armenia* or azerbaijan* or bangladesh* or belize* or benin* or bhutan* or bolivia* or "bosnia and herzegovina" or brazil* or bulgaria* or burkina faso* or burundi* or cabo verde* or cambodia* or cameroon* or central african republic* or chad* or china* or colombia* or comoros* or democratic republic congo* or congo republic* or costa rica* or "cote d'ivoire" or cuba* or djibouti* or dominica* or dominican republic* or ecuador* or egypt* or united arab republic* or el salvador* or equatorial guinea* or eritrea* or eswatini* or ethiopia* or fiji* or gabon* or gambia * or "georgia republic" or ghana* or grenada* or guatemala* or guinea* or guinea bissau* or guyana* or haiti* or honduras* or india* or indonesia* or iraq* or jamaica* or jordan* or kazakhstan* or kenya* or "democratic people's republic of korea" or kosovo* or kyrgyz republic* or lao pdr* or lebanon* or lesotho* or liberia* or libya* or madagascar* or malawi* or maldives* or mali* or marshall islands* or mauritania* or mauritius* or mexico* or micronesia fed sts* or mongolia* or montenegro* or morocco* or mozambique* or myanmar* or namibia* or nepal* or nicaragua* or niger* or nigeria* or north macedonia* or pakistan* or panama* or papua new guinea* or paraguay* or peru* or philippines* or romania* or russian federation* or rwanda* or samoa* or "sao tome and principe" or senegal* or serbia* or sierra leone* or solomon islands* or somalia* or south africa* or south sudan* or sri lanka* or "st. lucia" or "st vincent and the grenadines" or sudan* or suriname* or syrian arab republic* or tajikistan* or tanzania* or thailand* or timor leste* or togo* or tonga* or tunisia* or turkey* or turkmenistan* or tuvalu* or uganda* or ukraine* or uzbekistan* or uzbek* or vanuatu* or vietnam* or "west bank and gaza" or yemen rep* or zambia* or zimbabwe*).ti,ab,sh,kf.

19 17 and 18

20 limit 19 to english

WEB OF SCIENCE (CORE COLLECTION)

SEPTEMBER 23, 2022

1: TS=("air quality" OR "air toxic*" OR “traffic-related pollution” OR (Air AND (pollut* OR emission* OR exhaust OR particulate OR particle OR "black carbon" OR "nitrous oxide" OR "oxides of nitrogen" OR "nitrogen dioxide" OR "NO2" OR smoke OR "wood burn*" OR "wood heat*" OR fire-place OR fireplace OR chimney OR stack OR "tunnel" OR "PM10" OR "PM2.5")))

2: TS=(ambient* OR outdoor*)

3: #1 AND #2

4: TS=(Asthma* OR dyspnoea* OR dyspnea* OR cough* OR wheez* OR "respiratory sound*")

5: #3 AND #4

6: TS=(afghanistan* OR albania* OR algeria* OR american samoa* OR angola* OR argentina* OR armenia* OR azerbaijan* OR bangladesh* OR belize* OR benin* OR bhutan* OR bolivia* OR "bosnia and herzegovina" OR brazil* OR bulgaria* OR burkina faso* OR burundi* OR cabo verde* OR cambodia* OR cameroon* OR central african republic* OR chad* OR china* OR colombia* OR comoros* OR democratic republic congo* OR congo republic* OR costa rica* OR "cote d’ivoire" OR cuba* OR djibouti* OR dominica* OR dominican republic* OR ecuador* OR egypt* OR united arab republic* OR el salvador* OR equatorial guinea* OR eritrea* OR eswatini* OR ethiopia* OR fiji* OR gabon* OR gambia * OR "georgia republic" OR ghana* OR grenada* OR guatemala* OR guinea* OR guinea bissau* OR guyana* OR haiti* OR honduras* OR india* OR indonesia* OR iraq* OR jamaica* OR jordan* OR kazakhstan* OR kenya* OR "democratic people’s republic of korea" OR kosovo* OR kyrgyz republic* OR lao pdr* OR lebanon* OR lesotho* OR liberia* OR libya* OR madagascar* OR malawi* OR maldives* OR mali* OR marshall islands* OR mauritania* OR mauritius* OR mexico* OR micronesia fed sts* OR mongolia* OR montenegro* OR morocco* OR mozambique* OR myanmar* OR namibia* OR nepal* OR nicaragua* OR niger* OR nigeria* OR north macedonia* OR pakistan* OR panama* OR papua new guinea* OR paraguay* OR peru* OR philippines* OR romania* OR russian federation* OR rwanda* OR samoa* OR "sao tome and principe" OR senegal* OR serbia* OR sierra leone* OR solomon islands* OR somalia* OR south africa* OR south sudan* OR sri lanka* OR "st. lucia" OR "st vincent and the grenadines" OR sudan* OR suriname* OR syrian arab republic* OR tajikistan* OR tanzania* OR thailand* OR timor leste* OR togo* OR tonga* OR tunisia* OR turkey* OR turkmenistan* OR tuvalu* OR uganda* OR ukraine* OR uzbekistan* OR uzbek* OR vanuatu* OR vietnam* OR "west bank and gaza" OR yemen rep* OR zambia* OR Zimbabwe*)

7: #5 AND #6

8: #7 and English (Languages)

Appendix 2. ROBINS-E tool of the risk of bias assessment

Appendix Table B. ROBINS-E tool of the risk of bias assessment

Study	**Domain**	**Risk**	**Overall assessment**
Yan et al., (2022)	Confounding	Clinically relevant confounders were included in the analysis model	Low
	Exposure classification	Satellite based spatiotemporal model was used.	Low
	Participant selection	This study used a population-based large cohort from four cities in Northern China	Low
	Departure from intended exposure	The estimated annual mean concentration was based on the daily monitoring date. The concentration of $PM_{2.5}$ was treated as a time-varying variable	Low
	Missing data	This study had a few participants excluded due to missing covariates	Moderate
	Outcome measurement	Self-report and doctor diagnosis	Low
	Selection of reported result	No issue of selection of reporting was found	Low
Bagula et al., (2021)	Confounding	This study did not have data on the BMI and socioeconomic status of the participants	Moderate

	Exposure classification	Land-use regression model and geographic information system (GIS) were used to evaluate the spatial variation in the annual average concentrations	Low
	Participant selection	This study is a cross-sectional design but part of the larger cohort study from four informal settlements	Low
	Departure from intended exposure	The 1-year average concentration of pollutants	Low
	Missing data	NA	
	Outcome measurement	Self-reported and doctor-diagnosed asthma was used for the diagnosis of asthma	Low
	Selection of reported result	No issue of selection of reporting was found	Low
Ai et al., (2019)	Confounding	All clinically relevant confounders were included in the analysis model	Low
	Exposure classification	A combination of Aerosol Optical Depth (AOD) measurements and the Global Chemical Transport Models (CTMs) were used to estimate the yearly average concentrations of $PM_{2.5}$	Low
	Participant selection	A multistage cluster sampling method of the population-based cohort from six countries was used	Low
	Departure from intended exposure	The 3-year average concentration of $PM_{2.5}$ before the survey was used as the proxy for long-term exposure to $PM_{2.5}$	Moderate
	Missing data	NA	

	Outcome measurement	Self-report and medically diagnosed asthma were used for asthma diagnosis	Low
	Selection of reported result	No issue of selection of reporting was found	Low
Khafaie et al., (2017)	Confounding	This study did not include data on the socioeconomic status of the participants	Moderate
	Exposure classification	The atmospheric dispersion model, AERMOD to estimate background PM_{10} concentration	Low
	Participant selection	This study only included diabetic participants, DM, and non-diabetic hospital staff	High
	Departure from intended exposure	The annual mean concentration of PM_{10}	Low
	Missing data	Significant exclusion of participants due to the absence of valid lung functions	High
	Outcome measurement	A questionnaire and medical history of the respiratory symptoms of the participants were used for the diagnosis	Low
	Selection of reported result	No issue of selection of reporting was found	Low
Kumar et al., (2004)	Confounding	There was no data on the BMI of the participants	Moderate
	Exposure classification	A high-volume air sampler at a rate of 1 I/min was used for laboratory analysis	Low
	Participant selection	A cluster sampling design was used with a random selection of the colonies	Low

	Departure from intended exposure	A town-based air pollution exposure and not individual sampling	High
	Missing data	There was no significant exclusion of participants owing to missing data	Low
	Outcome measurement	British Medical Research Council Questionnaire was used to diagnose cough and wheezing	Low
	Selection of reported result	No issue of selection of reporting was found	Low
Chhabra et. al., (2001)	Confounding	NA	
	Exposure classification	Permanent air quality monitoring stations	Low
	Participant selection	A cross-sectional study with a randomized stratified sampling method was used	Low
	Departure from intended exposure	The 10-year average concentration of pollutants, and not individual exposure	Moderate
	Missing data	NA	
	Outcome measurement	A questionnaire was used for the diagnosis of wheezing, cough, and dyspnoea	Low
	Selection of reported result	No issue of selection of reporting was found	Low

$PM_{2.5}$ = particulate matter with an aerodynamic diameter of 2.5 µm or less, PM_{10} = particulate matter with an aerodynamic diameter of 10 µm or less, NO_2 = nitrogen dioxide, NA= Not Applicable, DM= Diabetes Mellitus, BMI= Body Mass Index

Appendix 3. Exposures, outcomes, exposure estimates, and covariates adjusted of the included studies.

Appendix Table C. **Exposures, outcomes, exposure estimates and covariates adjusted of the included studies.**

Study	**Exposure**	**Exposure information source**	**Outcome definition**	**Exposure estimates**	**Fully adjusted association (95%CI) reported**	**Covariate adjusted**
Yan et al., (1)	$PM_{2.5}$	Satellite-based spatiotemporal model with resolution 1 km x 1 km	Self-report and physician diagnosis of asthma	The average concentration of annual-mean $PM_{2.5}$ exposure from 2000 to 2009 was 66.5 µg/m$^{3.}$ (R^2=0.93 at monthly level and R^2=0.95 at annual level)	OR per 10 µg/m^3 increase in $PM_{2.5}$ was (1.36 95% CI 1.15, 1.60)	Age, gender, BMI, monthly income, education level, smoking status, passive smoking, physical activity, alcohol intake, family history of related chronic respiratory diseases
Bagula et al., (2)	$PM_{2.5}$, NO_2	Land-use regression (LUR) model and geographic information system (GIS) to assess the	Self-report and doctor diagnosis of asthma	**NO_2:** mean annual concentration was 16.9µg/m^3 (interquartile range:	OR for interquartile range increase of 14.1µg/m^3 in **NO_2** was (1.13 95% CI 0.11, 12.05) and	Age, sex, education, employment status, smoking status, physical activity

		annual average concentrations.		9.6µg/m^3 to 23.7 µg/m^3 **$PM_{2.5}$:** mean annual concentration was 10.1µg/m^3 (interquartile range: 7.3µg/m^3 to 12.4 µg/m^3	5.12µg/m^3 in **$PM_{2.5}$** was (1.27 95% CI 0.95, 1.71) in the single-pollutant model	
Ai et al., (3)	$PM_{2.5}$	A combination of Aerosol Optical Depth (AOD) measurements with the Global Chemical Transport Models (CTMs) to estimate the yearly average concentrations of $PM_{2.5}$ during 2007-2010 at 1 km x 1 km resolution. Original AOD data was	Participants who reported treatment for asthma within one year and /or those diagnosed with asthma from approved medical institutions. Validation through medical testing to establish the credibility of the	The mean SD for $PM_{2.5}$ (µg/m^3) for asthma and non-asthma participants were 37.33 (2.05) and 34.33 (2.02).	For each 10 µg/m^3 increase in **$PM_{2.5}$**, the adjusted RR for asthma is (1.05 95% CI 1.01, 1.08)	Age, sex, BMI, education, smoking status, alcohol consumption, and occupational exposure

		refined from 10 km x 10 km resolution to 1 km x 1 km resolution	data from self-reported patients.			
Khafaie et al., (4)	PM_{10}	Atmospheric dispersion model AERMOD to estimate background PM_{10} concentration at subject's home and work. PM_{10} at home x time stay at home/24 + PM_{10} at home x time stay at work/24	**Cough:** cough or phlegm that is not common cold that has been accumulating for at least three months of the year for the last two years. **Dyspnoea:** also referred to as shortness of breath is any attack of breath shortness except common colds occurring in the last twelve years.	Logistic regression models were used to describe the association between residential air pollution exposure and chronic respiratory symptoms. This was expressed as 1 SD = 98.38 µg/m3 of PM_{10} concentration (OR = expo [coef. X 98.38])	OR for 1 SD µg/m^3 increment in PM_{10} **Cough:** (1.33 95% CI 1.02-1.74) **Dyspnoea:** (1.50 95% CI 1.12, 2.01)	Age, gender, BMI, diabetes status, smoking, and temperature on the day of the blood sample collection
Kumar et al., (5)	PM_{10}, NO_2	Air sampling was conducted for at	Cough and wheezing for more	Exposure assessment	The OR for having chronic respiratory	Age, gender, education,

		least one day each week for 12 hours in each town using a high-volume air sampler at a rate of 1 l/min placed at a height of 10 feet	than one month using British Medical Research Council Questionnaire and spirometry test.	information was from collected from ecological source using logistic regression analysis to assess the effect of residence in a poor air-quality town on respiratory health.	symptoms was (1.5 95% CI 1.2, 1.8) **Cough:** (1.73 95% CI 1.29, 2.32) **Wheezing:** (1.89 95% 1.40, 2.55)	occupation, income, smoking status, passive smoking, type of cooking fuel, migration
Chhabra et al., (6)	NO_2		**Cough:** cough that happened on most days for three or more consecutive months during the year for the past two years. **Dyspnoea:** breathlessness on walking requiring the subject to stop or slow down for	Residential source of information	NR	Age, sex, economic status, smoking history, education, type of domestic fuel used, and occupation

breath when walking one's own pace on level ground. **Wheezing:** wheezing or whistling sounds in breathing associated with breathlessness on most days or nights

Abbreviations: R^2 means the coefficient of determination, which indicates how well the fitted regression model explains the actual data from measurement; SD, standard deviation; BMI, body mass index; OR odds ratio; RR, relative risk; NR, not reported.

Appendix 4. Completed PRISMA Checklist

Appendix Table D. Completed PRISMA Checklist

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
TITLE			1
Title	1	Identify the report as a systematic review.	
ABSTRACT			2
Abstract	2	See the PRISMA 2020 for the Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Appendix (1-3)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses.	7

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
Study	16a	Describe the results of the search and selection process, from the number of records identified in the search to the	29

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
selection		number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	30
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.	31
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	31
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	30
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate	31

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
		and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	32
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13-18
	23b	Discuss any limitations of the evidence included in the review.	19
	23c	Discuss any limitations of the review processes used.	19-21

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
	23d	Discuss the implications of the results for practice, policy, and future research.	22-23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including the register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to the information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
Competing interests	26	Declare any competing interests of review authors.	24
Availability of data, code, and	27	A report of which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Section and Topic	Item #	Checklist item	The location where the item is reported (page)
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 For more information, visit: http://www.prisma-statement.org/

Appendix 5. Data extraction form for included studies

Appendix Table E. Data extraction form for included studies

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g., Smith 2001)*	
Report ID	
Report ID of other reports of this study	
Notes	

General Information	
Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	

Publication type *(e.g. full report, abstract, letter)*	
Journal/issue of publication	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes No Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study design	Cohort	☐ ☐ ☐	
	Cross-sectional	☐ ☐ ☐	
Participants	Adults 18 years and above	☐ ☐ ☐	

Types of exposures	Air or gaseous pollutants such as PM_{10}, $PM_{2.5}$, NO_2, and black carbon.	☐ ☐ ☐	
Types of comparison	Cohort and cross-sectional studies reported on exposure to relatively low levels of air or gaseous pollutants in the same population.	☐ ☐ ☐	
Types of outcome measures	Asthma, wheezing, cough, and dyspnea	☐ ☐ ☐	
Types of effect estimates	Relative Risk (RR), Odds Ratio (OR), Hazard Ratio (HR)	☐ ☐ ☐	
	INCLUDE ☐ EXCLUDE ☐		
Reason for exclusion			
Notes:			

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Aim of study		
Study design		
Start date		
End date		
Number of participants per group		
Number of participants with the outcome		
Duration of participation *(from recruitment to last follow-up)*		
Notes:		

Adapted from https://training.cochrane.org/sites/training.cochrane.org/files/public/uploads/resources/downl oadable_resources/English/Collecting%20data%20-%20form%20for%20RCTs%20and%20n on-RCTs.doc

Appendix 6. A systematic review protocol.

Long-term exposure to outdoor air pollution and asthma in low-and middle-income countries: a systematic review protocol

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Funding: This study will not be receiving any funding.

Competing interests: The authors declare that no competing interests exist.

Data availability: Data will be available upon the study's completion.

Abstract

Background: Several epidemiological studies have examined the risk of asthma and respiratory diseases in association with long-term exposure to outdoor air pollution. However, little is known regarding the adverse effects of long-term exposure to outdoor air pollution on the development of these outcomes in low- and middle-income countries (LMICs). Our study aims to investigate the association between long-term exposure to outdoor air pollution and asthma and respiratory diseases in LMICs through a systematic review with meta-analysis.

Methods: This systematic review and meta-analysis will follow the PRISMA (Preferred Reporting for Systematic Reviews and Meta-Analyses) checklist and flowchart guidelines. The inclusion

criteria that will be used in our study are 1) Original research articles with full text in English; 2) Studies including adult humans; 3) Studies with long-term air pollution assessment in LMICs, air pollutants including nitrogen oxide (NO_2), sulfur oxide (SO_2), particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO) and ozone (O_3); 4) cohort and cross-sectional studies; 5) Studies reporting associations between air pollution and asthma and respiratory symptoms. A comprehensive search strategy will be used to identify studies published up till August 2022 and indexed in Embase, Medline, and Web of Science. Three reviewers will independently screen records retrieved from the database searches. Where there are enough studies with similar exposure and outcomes, we will calculate, and report pooled effect estimates using meta-analysis.

Systematic review registration: PROSPERO CRD42022311326

Discussion: Findings from the health effects of long-term exposure to outdoor air pollution may be of importance for policymakers. This review will also identify any gaps in the current literature on this topic in LMICs and provide direction for future research.

Introduction

Outdoor air pollution is a major menace to public health globally (1) that causes around 4.2 million deaths each year and inflicts a heavy morbidity burden on society (2, 3). Sweileh and co-workers (1) pointed out that almost 90% of deaths related to air pollution happen in low- and middle-income countries (LMICs) with almost 2 out of 3 happening in South-East Asia and Western Pacific regions. The World Health Organization (WHO) reports that 99% of the global population lives in regions where the recently launched WHO guideline limits on air pollution are exceeded (3, 4). South and East Asian locations emerge as the most polluted globally. Bangladesh, China, India, and Pakistan share 49 of the 50 most polluted cities worldwide. This high air pollution rate in Asia can be related to expeditious urbanization and industrialization (1, 5). In other areas such as the African Continent, there is no sufficient documentation on the magnitude of the attributable risk of outdoor air pollution (6, 7). The problem of air pollution is particularly severe in countries with social disparities and a lack of sustainable management of the environment (8).

Duan and co-workers (9) showed that even though the levels of air pollution in high income countries have significantly decreased over the last 25 years, over the same period, air pollution levels are on the increase in LMICs especially China and India.

In recent years, there has been an increase in knowledge about health effects of long-term air pollution exposures, especially on asthma and respiratory symptoms. In several countries, the prevalence of asthma is between 1 and 8% of the population. A recent study has shown that 13% of global incidence of asthma in children can be attributable to traffic-related air pollution (TRAP) and TRAP affects the development of asthma also in adults (10). In 2019, WHO reported that about 262 million persons had asthma which caused 461,000 deaths annually. Most asthma-related deaths happen in LMICs due to challenges of under-diagnosis and under-treatment (11). The WHO (11) further stressed the impact of asthma on normal daily living as it causes poor concentration, sleep disturbance, and tiredness during the day among persons not sufficiently treated for their asthma. Also, people who suffer from asthma and their families face the challenges of missing school and work, thus causing a substantial economic burden on their families and society at large.

Asthma is described as chronic inflammatory disorder of the airways associated with bronchial hyper-responsiveness, and reversible airflow limitation (5, 10, 12). In other words, asthma occurs when the air passage in the lungs narrows because of inflammation and tightening of the muscles around the small airways. The main symptoms of asthma are wheeze, dyspnea, cough, tightness of the chest and shortness of breath.

Air pollution may induce or aggravate asthma. Pollutants in the atmosphere are linked with increased incidence, prevalence, hospitalizations, or worsening symptoms of asthma (12). Tiotiu and co-workers (10) have further acknowledged that air pollution does not only worsen existing asthma but may cause new onset of asthma in previously healthy persons.

Even though both the air pollution burden and asthma disease burden are highest in LMICs, more systematic overviews from LMICs are scarce. One recent overview examined air pollution in LMICs in association with respiratory mortality and chronic obstructive pulmonary disease (COPD) (13), and one overview has examined air pollution in LMICs in association with asthma in children (14), but no overview currently exists covering air pollution and asthma in adults in LMICs. Such overviews could be important tools to improve public health by providing the basis for informed policy making and stimulating public health institutions and authorities to put more effective measures in place to reduce exposure to air pollutants. Thus, the main aim of this systematic review is to investigate the association between long-term health effects of outdoor air pollution and asthma and respiratory symptoms among adults over 18 years old in LMICs.

Materials and Methods

The proposed systematic review and meta-analysis will be conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (S1 Table) and flowchart guidelines (15). The study protocol was registered in advance in International Prospective Register of Systematic Reviews (PROSPERO- CRD42022311326).

Objective

The main objective of this review is to investigate the association between long-term health effects of outdoor air pollution and asthma and respiratory symptoms among adults (over 18 years old) in LMICs.

Review question

Does long-term exposure to outdoor air pollution increase the risks of asthma, and respiratory symptoms among adults (over 18 years old) in LMIC as compared to adults (over 18 years old) with relatively low levels of exposure to outdoor air pollution?

Eligibility Criteria

As pointed out by Schaefer and Mayers (16), documentation of clear criteria for inclusion and exclusion in any study is a major strength of the systematic review approach because it documents the reason why particular studies were selected as likely key studies and why other studies were excluded. These criteria are formed in accordance with the questions that are established during the problem formulation stage. In addition, eligibility criteria are conducted according to the Population (animal species inclusive), Exposure, Comparator, Outcomes, and Timing (PECOT) approach, study design, and date. Main exclusion criteria are unrelated studies, duplicates, full texts unavailability, or abstract-only papers while inclusion criteria entail studies on the target population, investigated exposure, or the comparison between two studied exposures. In a nutshell, the inclusion criteria should be articles that contain clear and sufficient information (both positive and negative) that answers the research question (17). Based on this definition of eligibility criteria, we identified our inclusion and exclusion criteria for this study

Inclusion criteria

- **Population:** Studies on human adult population on long-term exposure to outdoor air or gaseous pollutants (long-term defined as ≥1 year in line with the 2021 WHO air quality guidelines (18)) in LMICs.
- **Exposure:** Studies that reported on exposure to the outdoor air or gaseous pollutants nitrogen oxide (NO_2), sulphur oxide (SO_2), particulate matter (PM_{10}), particulate matter ($PM_{2.5}$), carbon monoxide (CO) and/or ozone (O_3).
- **Comparator:** Cohort studies that reported on exposure to relatively low levels of air or gaseous pollutants in the same population.
- **Outcomes:** Outcomes are asthma, and respiratory symptoms (such as wheeze, cough, and dyspnoea) that are not a result of biological agents.
- **Timing:** Studies conducted up to August 2022.

Exclusion criteria

Studies published in any other language besides English will not be included. Also, studies that are not available in full texts and studies conducted among participants less than 18 years old will not be considered.

Information sources

A significant component of the systematic review process is sufficient searching of scientific and relevant literature, hence, the suggestion of Schaefer and Mayers (16) that search terms should be carefully chosen to adequately narrow down the search results to produce rich information will be adhered to in this review.

As advised by Cheung and Vijayakumar (19) it is wise to search more than one database in order to reduce selection bias, thus, studies published in English up to August 2022 that matched the

PECOT question will be searched systematically in Embase (Ovid), Medline (Ovid), and Web of Science (Core collection). The aforementioned databases were selected to avoid too many duplications of studies from similar databases such as PubMed, Embase, and the Cochrane Library. Furthermore, a librarian from the faculty of medicine at the university will guide the search.

Search strategy

A pilot search of Embase (Ovid) was carried out to identify studies on the topic. The text words in the titles and abstracts of relevant studies and the index terms used to define the articles were used to develop a full search strategy (S2 Table). The reference lists of key full text articles included in the review will be screened to find additional studies. This review will conduct searches for relevant literature on the identified databases through a combination of free text and indexed terms such as Medical Subject Headings (MeSH) terms and will be combined using Boolean operators.

Data management

The search results will be compiled in a reference manager program using EndNote and duplicates will be removed. The records will further be exported to Rayyan software (20) where the screening of all records will be done.

Selection process

For a thorough review, three reviewers will independently screen all records retrieved from the database searches using Rayyan, a software for systematic reviews by screening the titles, and abstracts using screening question according to the inclusion and exclusion criteria. Full text articles will then be assessed by the same reviewers. Any disagreements between the three independent reviewers will be resolved through group discussion and voting or by contacting the author if further information is required. Reasons for exclusion of the articles will be recorded.

A PRISMA flowchart as shown in (S1 Figure) representing the selection process and numbers of the selected articles, the numbers of the articles initially identified, the numbers of articles excluded before and after screening based on titles and abstracts, eligible articles did not meet inclusion criteria, and the primary reasons for exclusion (15) will be presented.

Data collection process

Data from full texts will be extracted and screened by exporting the results to Excel form designed by the reviewers. The extraction characteristics of the included articles will be: name of authors; year, journal/issue of publication; study location; study design; sample size of the study; demographic characteristics of the study population; pollutants; outcomes; statistical methods; effect estimates; confounders in the statistical model (21, 22). In accordance with good practice, a pilot testing of the Excel form will be done on a sample of included studies to ensure that all relevant information is captured (23). The three reviewers will compare and discuss the accuracy and completeness of the data extracted. If during the extraction process some data is missing, unclear or incomplete, inquiries will be sent to the authors.

Risk of bias assessment

Three reviewers will independently assess the risk of bias in included by using the Risk of Bias In Non-randomized Studies-of Exposure (ROBINS-E) tool. The ROBINS-E tool developed by the ROBINS-E Development Group led by Higgins and co-workers (24) provides an orderly way to assess the risk of bias (RoB) in observational epidemiological studies. It includes seven domains of bias: confounding, exposure classification, participant selection, departure from intended exposure, missing data, and outcome measurement. Each domain is addressed using a series of signaling questions with the purpose of collecting significant information on the study and analysis being evaluated. In addition, three judgements are done after the important signaling questions have been answered, then, an overall judgement is carried out for each of these considerations (24). This tool was used by Park and co-workers (25) in a very simplified approach, thus making it adoptable for other researchers like us.

A pilot quality assessment will be conducted on a few selected included studies. It is anticipated that the quality assessment of studies could involve a certain extent of subjective judgment, thus, any differences in opinion will be resolved through discussion. The quality assessment for individual included studies will be qualitatively summarized as part of the summary of the findings table.

Analysis

Descriptive analysis

We will conduct a narrative synthesis of the findings from the included studies. We will structure the narrative synthesis by describing the studies according to the study design; characteristics of the target population (e. g age, sex, socioeconomic status, educational level etc.); the type of air pollutants; the type of respiratory health outcomes.

Statistical analysis

If there are enough studies with similar exposure and outcomes, we will pool the results using meta-analysis in the STATA software. As described by Cheung and Vijayakumar (19) and Lee (26), two statistical models are used for a meta-analysis given that a meta-analysis merges the effect sizes of the included studies by weighting the data in accord with the diverse amounts of data in each study. On one hand, the fixed effect model infers that all the studies in the meta-analysis have one true effect size and the observed variation amongst studies is due to sampling errors or chance. The fixed effect model evaluates only intra-study sampling errors, that is, intra-study variation. On the other hand, the random effect model assumes that various studies display considerate diversification, and the true effect size might range between studies. It also evaluates both intra-study sampling errors and inter-study variance, that is, between-study variation.

With the understanding of which model to use as described by Lee above, the DerSimonian and Laird random-effects methods for meta-analysis might be employed. This is in line with other systematic reviews and meta-analyses related to this topic of interest (21, 25, 27, 28, 29). Furthermore, DerSimonian and Laird random effects model has been known to be the simplest and most widely used method for fitting the random effects model for meta-analysis (30). Heterogeneity among studies will be assessed using both the $\chi2$ test and I^2 statistics. According to the Cochrane Handbook (31), we will consider an I^2 value over 50% to indicate substantial heterogeneity. We will assess publication bias by using funnel plots and Egger's linear regression.

Assessment of certainty of evidence across studies

For each pollutant exposure and outcome, the certainty of evidence (CoE) will be judged by adapting the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE domains consist of risk of bias, directness of information, precision of an estimate, consistency of estimates across studies, risk of bias related to selective reporting, strength of the association, presence of a dose-response gradient, and the presence of plausible residual confounding that can increase confidence in estimated effects (32). The basis of the GRADE domains assessment will be from the results of the risk RoB assessment, heterogeneity, sensitivity, and publication bias analyses (21, 33). The overall rating of certainty of evidence as described by (28) are as follows;

- High: means there is unlikely change in the effect estimate given further studies.
- Moderate: a certain likelihood in change of the effect estimate given further studies.
- Low: further studies are very likely to cause a change in the effect estimate.

- Very low: high uncertainty in the effect estimate.

Discussion

This systematic review protocol was precisely developed to increase the knowledge and awareness on deleterious air or gaseous pollutants that cause obstructive respiratory diseases such as asthma and respiratory symptoms to support the drive for future research. There is growing evidence of the positive association between some air or gaseous pollutants and the development of respiratory diseases in high-income countries. However, very few studies have been conducted in the low-and middle-income countries on the significant association between air or gaseous pollutants and respiratory diseases. Hence, we aim to investigate the association between long-term health effects of outdoor air pollution and asthma and respiratory symptoms among adults (over 18 years old) in LMICs. This evidence will provide institutional bodies with a better prospect to regulate and formulate measures on air pollution to prevent unfavorable health outcomes in these countries.

Conclusions

The findings from this review will contribute to the growing body of knowledge of the health effects of outdoor air pollution and may hopefully be used to inform policymaking in LMICs-contributing to improving public health in these areas.

Author Contributions

Conceptualization: Achenyo Peace Abbah, Shanshan Xu, Ane Johannessen

Methodology: Achenyo Peace Abbah, Shanshan Xu, Ane Johannessen

Supervision: Shanshan Xu, Ane Johannessen

Writing – original draft: Achenyo Peace Abbah

Writing- review & editing: Achenyo Peace Abbah, Shanshan Xu, Ane Johannessen

Acknowledgements

We would like to acknowledge the contribution of Elisabeth Ebner for her assistance with the electronic pilot search strategy.

Supporting information

S1 Table. Completed PRISMA-P Checklist. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 checklist: recommended items to address in a systematic review protocol.

S2 Table. Search strategy

S1 Fig. PRISMA flowchart of the study identification and selection process

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Appendix 7. Supporting information for systematic review protocol

S1 Table. Completed PRISMA-P Checklist. Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No		Checklist item
			ADMINISTRATIVE INFORMATION
Title:			
Identification	1a	√	Identify the report as a protocol of a systematic review
Update	1b	N/A	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	√	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	√	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	√	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	N/A	Indicate sources of financial or other support for the review
Sponsor	5b	N/A	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	N/A	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
			INTRODUCTION
Rationale	6	√	Describe the rationale for the review in the context of what is already known
Objectives	7	√	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
			METHODS
Eligibility criteria	8	√	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	√	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	√	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Study records:			
Data management	11a	√	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	√	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	√	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	√	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	√	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	√	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	√	Describe criteria under which study data will be quantitatively synthesised
	15b	√	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	√	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	√	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	√	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	√	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

S2 Table. Search strategies

Embase Ovid

1 Air Pollution/

2 smoke/ or soot/

3 Vehicle Emissions/

4 exp Air Pollutants/

5 Ozone/

6 Nitrogen Dioxide/

7 ("air quality" or "air toxic*" or (Air and (pollut* or emission* or exhaust or lead or diesel or particulate or particle or "elemental carbon" or "black carbon" or "carbon monoxide" or "nitrous oxide" or "oxides of nitrogen" or "nitrogen dioxide" or "sulfur dioxide" or ozone or lead or traffic or vehicle or road or bushfire or bush-fire or wildfire or wild-fire or "controlled burn" or smoke or "wood burn*" or "wood heat*" or fire-place or fireplace or chimney or stack or tunnel or "vent stack" or "light scatter*" or "back scatter*" or visibility or nephelometer or "coal dust" or "coal burn*"))).ti,ab,kw.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 (ambient or outdoor*).ti,ab,kw.

10 8 and 9

11 Asthma/

12 Respiratory Sounds/

13 (Asthma* or dyspnea* or dyspnoea* or "shortness of breath" or "breath shortness" or breathlessness or "respiratory sound*" or "breathing sound*" or "lung sound*" or wheez*).ti,ab,kw.

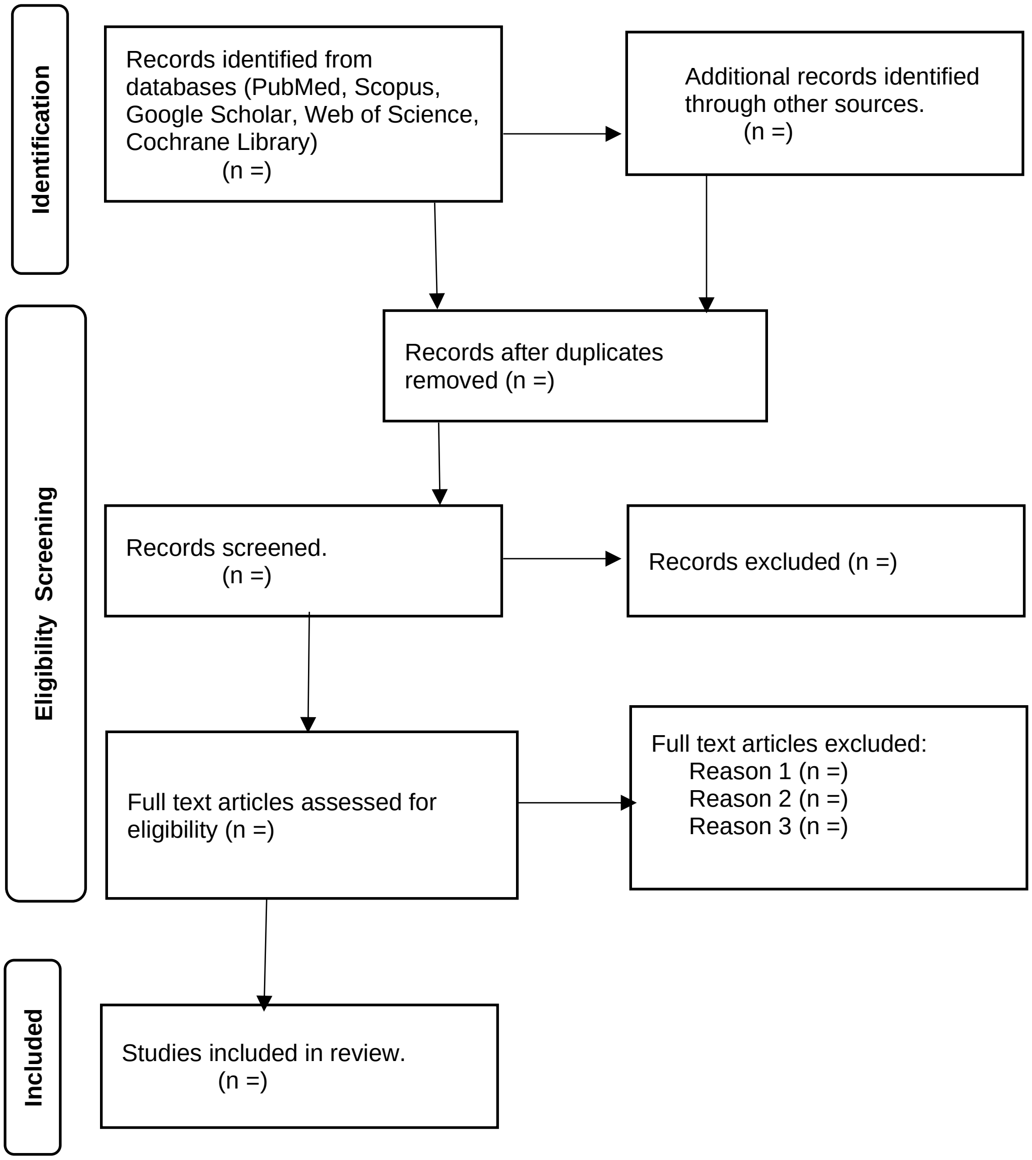
14 11 or 12 or 13

15 10 and 14

16 (afghanistan or albania or algeria or american samoa or angola or "antigua and barbuda" or antigua or barbuda or argentina or armenia or armenian or aruba or azerbaijan or bahrain or bangladesh or barbados or republic of belarus or belarus or byelarus or belorussia or byelorussian or belize or british honduras or benin or dahomey or bhutan or bolivia or "bosnia and herzegovina" or bosnia or herzegovina or botswana or bechuanaland or brazil or brasil or bulgaria or burkina faso or burkina fasso or upper volta or burundi or urundi or cabo verde or cape verde or cambodia or kampuchea or khmer republic or cameroon or cameron or cameroun or central african republic or ubangi shari or chad or chile or china or colombia or comoros or comoro islands or iles comores or mayotte or democratic republic of the congo or democratic republic congo or congo or zaire or costa rica or "cote d’ivoire" or "cote d’ ivoire" or cote divoire or cote d ivoire or ivory coast or croatia or cuba or cyprus or czech

republic or czechoslovakia or djibouti or french somaliland or dominica or dominican republic or ecuador or egypt or united arab republic or el salvador or equatorial guinea or spanish guinea or eritrea or estonia or eswatini or swaziland or ethiopia or fiji or gabon or gabonese republic or gambia or "georgia (republic)" or georgian or ghana or gold coast or gibraltar or greece or grenada or guam or guatemala or guinea or guinea bissau or guyana or british guiana or haiti or hispaniola or honduras or hungary or india or indonesia or timor or iran or iraq or isle of man or jamaica or jordan or kazakhstan or kazakh or kenya or "democratic people’s republic of korea" or republic of korea or north korea or south korea or korea or kosovo or kyrgyzstan or kirghizia or kirgizstan or kyrgyz republic or kirghiz or laos or lao pdr or "lao people's democratic republic" or latvia or lebanon or lebanese republic or lesotho or basutoland or liberia or libya or libyan arab jamahiriya or lithuania or macau or macao or republic of north macedonia or macedonia or madagascar or malagasy republic or malawi or nyasaland or malaysia or malay federation or malaya federation or maldives or indian ocean islands or indian ocean or mali or malta or micronesia or federated states of micronesia or kiribati or marshall islands or nauru or northern mariana islands or palau or tuvalu or mauritania or mauritius or mexico or moldova or moldovian or mongolia or montenegro or morocco or ifni or mozambique or portuguese east africa or myanmar or burma or namibia or nepal or netherlands antilles or nicaragua or niger or nigeria or oman or muscat or pakistan or panama or papua new guinea or new guinea or paraguay or peru or philippines or philipines or phillipines or phillippines or poland or "polish people's republic" or portugal or portuguese republic or puerto rico or romania or russia or russian federation or ussr or soviet union or union of soviet socialist republics or rwanda or ruanda or samoa or pacific islands or polynesia or samoan islands or navigator island or navigator islands or "sao tome and principe" or saudi arabia or senegal or serbia or seychelles or sierra leone or slovakia or slovak republic or slovenia or melanesia or solomon island or solomon islands or norfolk island or norfolk islands or somalia or south africa or south sudan or sri lanka or ceylon or "saint kitts and nevis" or "st. kitts and nevis" or saint lucia or "st. lucia" or "saint vincent and the grenadines" or saint vincent or "st. vincent" or grenadines or sudan or suriname or surinam or dutch guiana or netherlands guiana or syria or syrian arab republic or tajikistan or tadjikistan or tadzhikistan or tadzhik or tanzania or tanganyika or thailand or siam or timor leste or east timor or togo or togolese republic or tonga or "trinidad and tobago" or trinidad or tobago or tunisia or turkey or turkmenistan or turkmen or uganda or ukraine or uruguay or uzbekistan or uzbek or vanuatu or new hebrides or venezuela or vietnam or viet nam or middle east or west bank or gaza or palestine or yemen or yugoslavia or zambia or zimbabwe or northern rhodesia or global south or africa south of the sahara or sub-saharan africa or subsaharan africa or africa, central or central africa or africa, northern or north africa or northern africa or magreb or maghrib or sahara or africa, southern or southern africa or africa, eastern or east africa or eastern africa or africa, western or west africa or western africa or west indies or indian ocean islands or caribbean or central america or latin america or "south and central america" or south america or asia, central or central asia or asia, northern or north asia or northern asia or asia, southeastern or southeastern asia or south eastern asia or southeast asia or south east asia or asia, western or western asia or europe, eastern or east europe or eastern europe or developing country or developing countries or developing nation? or developing population? or developing world or less developed countr* or less developed nation? or less developed population? or less developed world or lesser developed countr* or lesser developed nation? or lesser developed population? or lesser developed world or under developed countr* or under developed nation? or under developed population? or under developed world or underdeveloped countr* or underdeveloped nation? or underdeveloped population? or underdeveloped world or middle income countr* or middle income nation? or middle income population? or low income countr* or low income nation? or low income population? or lower income countr* or lower income nation? or lower income population? or underserved countr* or underserved nation? or underserved population? or underserved world or under served countr* or under served nation? or under served population? or under served world or deprived countr* or deprived nation? or deprived population? or deprived world or poor countr* or poor nation? or poor population? or poor world or poorer countr* or poorer nation? or poorer population? or poorer world or developing econom* or less developed econom* or lesser developed econom* or under developed econom* or underdeveloped econom* or middle income econom* or low income econom* or lower income econom* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmics or third world or lami countr* or transitional countr* or emerging economies or emerging nation?).ti,ab,sh,kf.

17 15 and 16



S1 Fig. PRISMA flowchart of the study identification and selection process

Appendix 8. Response letter to Reviewers' comments

Dear PLOS ONE academic editor Dr Haruna Musa Moda and reviewers,

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled "Long-term health effects of outdoor air pollution on asthma and respiratory symptoms: a systematic review and meta-analysis" to *PLOS ONE*. We appreciate the time and effort that you have dedicated to providing your valuable feedback on our manuscript. We have carefully revised the manuscript according to the reviewers' insightful comments and have provided point-by-point responses as follows, and we have highlighted the changes within the manuscript. We greatly appreciate the Reviewers' comments, they enabled us to improve the quality of our paper substantially.

Journal Requirements:

When submitting your revision, we need you to address these additional requirements.

1. Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming. The PLOS ONE style templates can be found at https://journals.plos.org/plosone/s/file?id=wjVg/PLOSOne_formatting_sample_main_body.pdf and https://journals.plos.org/plosone/s/file?id=ba62/PLOSOne_formatting_sample_title_authors_affiliations.pdf

Response: We have adhered to the PLOS ONE's style requirements in the revised version of the manuscript

2. We note that the original protocol file you uploaded contains a confidentiality notice indicating that the protocol may not be shared publicly or published. Please note, however, that the PLOS Editorial Policy requires that the original protocol be published alongside your manuscript in the event of acceptance. Please note that should your paper be accepted, all content including the protocol will be published under the Creative Commons Attribution (CC BY) 4.0 license, which means that it will be freely available online, and any third party is permitted to access, download, copy, distribute, and use these materials in any way, even commercially, with proper attribution.

Response: We have removed the confidentiality notice from the revised version of the manuscript and have added a statement that we will be able to publish this protocol under CC BY 4.0.

Therefore, we ask that you please seek permission from the study sponsor or body imposing the restriction on sharing this document to publish this protocol under CC BY 4.0 if your work is accepted. We kindly ask that you upload a formal statement signed by an institutional representative clarifying whether you will be able to comply with this policy. Additionally, please upload a clean copy of the protocol with the confidentiality notice (and any copyrighted institutional logos or signatures) removed.

3. We noticed you have some minor occurrences of overlapping text with the following previous publication(s), which needs to be addressed:

- https://www.frontiersin.org/articles/10.3389/fped.2021.827507/full

In your revision ensure you cite all your sources (including your own works), and quote or rephrase any duplicated text outside the methods section. A further consideration is dependent on these concerns being addressed.

Response: We have not seen the review article on global research on perinatal palliative care that you refer to before. Any similarity and overlapping text with this paper is therefore due to chance. We suspect there will be some degree of overlapping text between all systematic review papers within the medical field, as there are many formal requirements to this kind of paper needs to adhere to. Please let us know if we need to revise any sections of our text due to this coincidence, we will of course be happy to oblige.

Comments from Reviewers

Reviewer #1:

Comment 1: *Make sure to accentuate the findings of the systematic review that relates to /answers the review question you stated in your protocol.*

Response: Thank you for pointing this out, we will indeed accentuate the findings relating to the review question in our systematic review and keep this protocol paper vivid in mind when performing the systematic review.

Reviewer #2: Detailed Review

The current manuscript details a study protocol for carrying out a systematic review of long-term exposure to outdoor air pollution and its links to asthma prevalence in low-and middle-income countries (LMIC).

General comment 1: *The English language in the manuscript needs to be more polished e.g., 1 - Refer to lines 61 to 63. The wordings are not right e.g., 2 - Instead of using Dual et al., Orlenno et al., and so forth in the paper, rewrite these sentences to bring in more uniformity for the reader.*

Response: Thank you for pointing this out. We agree with this comment and have gone through the manuscript rephrasing wordings in better English where needed to improve the reader's understanding.

e.g., 1: We have corrected the wording. The change can for example be found on page 3, paragraph 3, and lines 63-64.

e.g., 2- We have rewritten the sentences by incorporating the names of the authors using in-text Vancouver referencing style all through the manuscript (writing, for example, Duan and co-workers instead of Duan et al. on page 3, paragraph 2, and lines 60).

General comment 2: *Certain sections should be rewritten more concisely E.g. – Section on "Assessment of certainty of evidence across studies" Here, once the author expands the GRADE approach and cites appropriately, there is no need to write in detail and define it. One of the important purposes of citing/quoting references is to refer the reader to sources that can provide more information on the context being discussed and avoid detailing the concepts or procedures again.*

Response: Agree. We have, accordingly, revised this sentence and we have deleted the detailed description. We have made the changes on page 11, lines 235-237.

Major comment 1: *Lines 84-85 – Mentions systematic overview from LMICs is lacking. This definitely is an understatement as recent systematic reviews and meta-analyses are available on this topic (https://doi.org/10.1016/j.envres.2022.114604; https://doi.org/10.1016/j.atmosenv.2021.118422).*

Hence, the introduction needs to be rewritten with a better emphasis on the need for the current proposed review and how it is different/unique from other existing reviews on the topic.

Response: We thank the reviewers for the two review papers' recommendations. Our statement about how systematic overviews from LMICs are lacking refers to overviews on air pollution and asthma in adults. We agree this should be more clearly specified and have rewritten the Introduction accordingly. We have also included the two suggested references (page 4, lines 89-93).

Major comment 2: *Lines 249-251 - The expected outcomes of the review are overstated. How are the authors linking a review of this kind to directly inform policymaking?*

Response: we agree the expected outcomes may have been worded a bit too ambitiously, and we have revised the manuscript accordingly. Although systematic review papers such as our planned paper are indeed suitable to inform policymaking- through summarizing large amounts of information, identifying positive and negative effects of various exposures, and identifying gaps in medical research- we do not have a direct link with the policymakers in LMICs and can therefore not assume that our paper will directly inform policymaking. We have kept the potential for policymaking in the manuscript but have acknowledged that we cannot be certain that our paper will be used for this purpose (page 5, lines 93-98, page 12, lines 258-260, lines 262-264).

Major comment 3: *In their inclusion criteria, the authors mention "Long term" and "≥1 year". Typically, at least a period covering more than one annual cycle or with repetitive annual seasonal cycles are referred to as long term. Hence, use a different jargon or increase the exposure duration to "≥2 years" if feasible.*

Response: Although we agree that more than one annual cycle is ideal for looking at long-term exposures, the purpose of this planned systematic review is to gather an overview of all long-term air pollution exposure papers focusing on asthma in adults in LMICs. To not miss out on any papers, we have chosen the definition of long-term exposure from the 2021 WHO Global air quality guidelines. In these guidelines, long-term exposure is defined as "a mean of one or several years" while short-term exposure is "measures over minutes to days". We have specified the reason for our definition of long-term exposure in the revised manuscript (page 6, lines 128-129).

Minor comment 1: *Lines 36 to 42 – The historical statements given here are of little importance to the context. The authors should rewrite these in a better way leading the reader to the topic.*

Response: Thank you for pointing this out. We have, accordingly, changed the first paragraph in the introduction section for better understanding. This can be found on pages 2-3, lines 38-46.

Minor comment 2: *Lines 125-126 – "Outcomes that include asthma, respiratory symptoms" –*

Such outcomes can also result from biological agents. So care should be taken while screening articles and this needs to be explicitly mentioned in the inclusion/exclusion criteria

Response: Agree. Health outcomes that were identified in this systematic review are now explicitly mentioned in the inclusion/exclusion criteria. This can be found on page 6, lines 135-136.

Minor comment 3: *Introduce expanded forms of abbreviations before start using them (e.g., RoB)*

Response: We agree with this and have incorporated your suggestion throughout the manuscript. The expanded form of RoB can be found on page 11, and line 242.

Minor comment 4: *Please check for the appropriate use of subscripts and postscripts throughout the manuscript including the reference section.*

Response: We agree with this and have incorporated your suggestion throughout the manuscript. These changes can for example be found on page 13, lines 325, 350-355.

Minor comment 5: *The authors assume 18 years to be the universal adult age, and this is not true even within some LMIC countries. So, it's better to write it explicitly as 18 years through the manuscript in place of saying "adults"*

Response: We thank the reviewers for pointing this out. We have explicitly stated that we mean 18 years or above when referring to adults throughout the revised manuscript. These changes can for example be found on page 5, lines 106-107.