



Interventions to reduce the impact of outdoor air pollution on asthma: A systematic review

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Background. Exposure to air pollution can cause adverse health effects in people living with chronic lung disease. In people with asthma, it is not clear whether strategies to reduce outdoor air pollution can affect clinical symptoms and lung function.

Objectives. To determine strategies to reduce air pollution exposure for people with asthma, and to describe the effect of reduced air pollution on asthma outcome.

Methods. A systematic review was conducted of six databases for English literature. Any study published between April 2012 and March 2022 that mentioned air pollution exposure reduction and asthma was reviewed. Two reviewers (STH and RMp) screened and extracted the data separately, using a standardised form based on the Cochrane data extraction tool. Risk of bias was assessed using the risk-of-bias 2 tool. Outcome measures were the Asthma Control Test (ACT), the Childhood Asthma Control Test, exacerbations, and the forced expiratory volume in the 1st second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC ratio. The study was registered with PROSPERO (reg. no. CRD42022341648).

Results. Of the 11 116 identified studies, eight met the inclusion criteria, with a total of 11 395 043 participants. Clean air policy implementation modestly improved lung function, as shown by an increase in FVC and FEV₁ of 0.02 L/year and 0.01 L/year, respectively. Reduction of exposure to outdoor smoke pollution with use of mobile application alerts resulted in behavioural change and improved ACT scores over 8 weeks (mean (standard deviation (SD)) 21.5 (2.3) compared with baseline (20.0 (2.4); $p < 0.001$). Asthma control improved during low levels of pollution related to COVID-19 lockdown, as shown by mean (SD) ACT scores (17.3 (4.7) v. 19.7 (4.5); $p < 0.001$) and associated declines in mean daily hospital admissions (4.5 (3.4) days v. 2.8 (2.5) days; $p < 0.001$).

Conclusion. Air pollution is a major hazard, and strategies to reduce exposure have a positive outcome in terms of the asthma morbidity. This field would benefit from further high-quality randomised clinical trial evidence to inform policy and decision-making.

Keywords. Air quality, pollution, asthma, clean air, policy.

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Study synopsis

What the study adds. The prevalence and burden of asthma are increasing globally. Air pollution exposure is a major cause of worse asthma symptoms. Strategies to reduce air pollution or exposure to it may contribute towards improved quality of life. This study highlights potential strategies and their effect on asthma outcome.

Implications of the findings. A combination of individual activities and actions by governments to reduce air pollution can improve asthma outcome. A focus on education together with behavioural changes can reduce exposure at the individual level. Implementation of clean air policies reduces air pollution exposure and improves lung health

Asthma is one of the most common chronic diseases in children, adolescents and adults, leading to considerable morbidity and mortality worldwide.^[1-3] Approximately 300 million people globally, including ~10% of children, have asthma.^[4] Morbidity from asthma is highest in low- to middle-income countries where air quality is poor.^[5] Previous studies have shown that exposure to outdoor pollutants can worsen asthma control,^[6] and high outdoor pollution levels have been

associated with an increased risk of asthma in childhood.^[7] Children with high early-life air pollution exposures, particularly to traffic-derived pollutants, have an increased risk of a diagnosis of asthma during the preschool years.^[8]

Strategies to reduce air pollution levels include optimising driving style and vehicle settings, low emission zones, cleaner air fuel sources, and a more stringent regulatory environment to mitigate outdoor

pollution from industry and vehicle emissions.^[9] At the individual level, strategies that reduce exposure include use of close-fitting N95 particulate respirators, face masks, changing of walking/cycling routes, and air quality alerts and education to reduce traffic-related particulate matter ≤ 2.5 microns in diameter (PM_{2.5}) exposure.^[10-14] Choosing low-traffic routes can decrease exposure of cyclists and walkers to air pollutants, potentially reducing associated detrimental health effects.^[12] Air quality alerts and education influence a range of behaviour change outcomes, including self-efficacy, perception of risk, action planning and preventive behaviours.^[15,16]

We therefore conducted this systematic review to assess which strategies to reduce outdoor air pollution at an individual or community level can influence asthma outcomes in children, adolescents and adults.

Methods

Search strategy

The systematic review protocol was developed and registered with PROSPERO (reg. no. CRD42022341648). We used the Population, Intervention, Comparison, Outcomes and Time (PICOT) framework to aid with the systematic search. The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^[17] The following databases were searched: Clinical Trials Registry Platform and Cochrane Central Register of Controlled Trials (CENTRAL), EBSCOHost, PubMed, Science Direct, Scopus and Web of Science. We also conducted a search on low emission zone articles. Only scientific articles written in English published between 1 April 2012 and 31 March 2022 were included.

The search strategy was structured to include terms for 'air pollution', 'asthma', 'reduction strategy', 'reduction methods', 'asthma symptoms', 'asthma control test' and 'lung function test'. The full electronic search strategy is shown in Supplementary File 1 (available online at <https://www.samedical.org/file/2260>).

Selection of studies

Two reviewers (STH and RMp) independently screened articles identified by searching the electronic databases, using a three-stage review with initial search by title, followed by the abstract and then the full text. The full text of potentially eligible studies was evaluated against the review criteria to identify articles for inclusion. A third reviewer (RMa) was available at each stage in case of disagreements.

Inclusion and exclusion criteria

Studies were selected in accordance with the eligibility criteria (Table 1). All studies that focused on air pollution reduction interventions and their impact in people with asthma were included. Control groups were any in which participants had no air pollution exposure reduction. Eligible outcomes were improved asthma outcomes including symptom control as measured by the Asthma Control Test (ACT),^[18] the Childhood Asthma Control Test (c-ACT),^[18] asthma exacerbations, and lung function as measured by the forced expiratory volume in the 1st second (FEV₁), the FVC (forced vital capacity) and the ratio of FEV₁ to FVC. We included randomised controlled trials (RCTs) (e.g. parallel, cluster and crossover trials) and non-randomised studies that included a comparison treatment arm (i.e. any quantitative study that

investigated the effectiveness of an intervention aimed to assess our objectives and did not use randomisation to allocate participants to intervention or comparator groups – e.g. cohort studies or controlled before-and-after studies). Studies identified from searching electronic databases were combined and duplicates were removed. We excluded any grey literature from experts in the field, conference abstracts or unpublished material.

Data extraction and quality assessment

Data on study design, setting, population, authorship and statistical analysis were extracted from full texts of the included studies using a standardised form based on the Cochrane data extraction form^[19] (Supplementary File 2, <https://www.samedical.org/file/2261>). STH and RMp independently assessed the risk of bias for each study using the risk-of-bias 2 (RoB 2) tool.^[20]

Data analysis and synthesis

Owing to the heterogeneity of study designs, we could not perform a meta-analysis and summarised the data in a narrative. We therefore grouped the studies according to intervention and outcome.

Results

There were 11 116 articles identified through searching electronic databases (CENTRAL $n=3$, EBSCOHost $n=2\ 738$, PubMed $n=4\ 786$, Science Direct $n=2\ 925$, Scopus $n=254$ and Web of Science $n=410$). Of these, 2 852 duplicates were excluded and further 8 131 were excluded on title review. After further abstract screening, 118 were excluded. The remaining 15 were assessed for eligibility on full article review, of which 7 were excluded, leaving 8 for inclusion in the review (Fig. 1).

Characteristics of the interventions

Eight studies met the inclusion criteria, including two RCTs, with a total of 11 395 043 participants (Table 2). The ages of participants ranged from 0 to ≥ 65 years. Interventions included use of an air quality alert mobile application, implementation of emission reduction and adoption of clean air policies, lockdown measures during the COVID-19 pandemic, and an educational programme. The outcomes measured were asthma symptoms, ACTs, lung function tests, admission rates and emergency department (ED) visits.

Air quality alerts

In a population-based cohort study of introduction of an air quality alert programme in Toronto, Canada, using an online platform, there was some reduction in asthma symptoms.^[21] There was a strong effect for the air quality alert programme, with 4.7 fewer asthma-related ED visits per 1 000 000 people per day (95% confidence interval (CI) 0.55 - 9.38), or in relative terms a reduction of 25% (95% CI 1 - 47) in ED visits.^[21]

The Smoke Sense Urbanova (SSU) smartphone application forecasts visualisation of quality of air. An intervention with the SSU with additional alerts to maximise risk reduction on the application SSU Plus (SSU-P) in Washington State, USA, was studied.^[22] In an 8-week RCT with three study arms, i.e. SSU-P v. SSU and no intervention, there was a small but statistically significant increase in ACT scores at week 8 in the SSU-P arm (mean (standard deviation (SD)) 21.5 (2.3)) compared with baseline (20.0 (2.4); $p=0.0008$). There was no

difference in the ACT scores comparing the SSU with no intervention at week 8 (21.0 (4.0)) from baseline (21.3 (2.1)).^[22]

For the lung function test, surprisingly there was a decrease in FEV₁ percentage predicted in the SSU-P group at week 8 (mean (SD) 88.6% (17.2%)) compared with baseline (94.9% (16.2%); $p=0.0172$). This decrease was not found in the SSU arm, with a mean percentage predicted FEV₁ at week 8 of 95.6% (17.2%) compared with baseline (97.6% (14.6%); $p>0.05$). In the control arm, there was also no change in mean percentage predicted FEV₁ at week 8 (92.9% (16.0%)) compared with baseline (88.4% (20.2%); $p>0.05$).^[22]

Clean air policy implementation

Adar *et al.*^[23] studied the adoption of clean air technology and fuel policy compared with the pre-policy period in Washington State, USA. In this study, a natural experiment to examine associations between clean air technologies and fuels in school buses and children's health was conducted. The adoption of ultra-low-sulphur diesel was associated with small clinically meaningless increases in lung function, 0.02 (95% CI 0.003 - 0.05) L/yr for FVC and 0.01 (95% CI -0.006 - 0.03) L/yr for FEV₁. Although these associations were generally robust to control for multiple interventions, they had wide CIs and could not be distinguished from no association.^[23]

In Korea, the impact of implementation of air pollution emission reduction policies was assessed in the capital city, Seoul, and a metropolitan city, Daejeon.^[24] Air pollutant emissions were decreased during the study period. Total emissions in Seoul were relatively greater than those in Daejeon. A comparison of the two cities found an association between emission reductions and reduced ambient concentrations. Trends in hospital visit rates for asthma, which had previously been increasing in Seoul, decreased after the implementation of the policies. Prevented hospital visit cases for asthma in Seoul in the total population and the younger population (0 - 18 years) were estimated as 500 000 (11.3% of hospital visit cases if there was no intervention) and 320 000 (15.5% of hospital visit cases if there was no intervention), respectively.^[24]

Lockdown

A study in Riyadh, Saudi Arabia, that assessed the impact of the COVID-19 lockdown period on patients with severe asthma treated with biologics showed a change in mean (SD) ACT scores from 17.3 (4.7) before the lockdown to 19.7 (4.5) after 12 weeks of lockdown.^[25] This finding suggested significant improvement in the control of asthma, with a mean difference of 2.4 (3.7) ($p<0.001$). There was also an increase in the proportion of patients who were controlled before and after 12 weeks of lockdown (41% v. 60.7%). Levels of carbon monoxide, sulphur dioxide and nitrogen dioxide were all shown to decrease in Riyadh region compared with the months before the lockdown. All these pollutants are directly linked to the traffic and industrial activity in the area.^[25]

A study assessing ambient air pollutant concentrations and asthma-related hospital admissions during COVID-19 transport restrictions found improvements in air quality in Dublin, Ireland. During the period of transport restrictions, there was a significant decrease in mean daily concentrations of both PM_{2.5} (8.9 v. 7.8 $\mu\text{g}/\text{m}^3$; $p=0.002$) and nitrogen dioxide (24.0 v. 16.7 $\mu\text{g}/\text{m}^3$; $p<0.001$).^[26] There

was a statistically significant reduction in average daily admissions for asthma (mean (SD) 4.5 (3.4) v. 2.8 (2.5); $p<0.001$). There was also a statistically significant reduction in inpatient median (interquartile range) bed days (6.0 (2.0 - 14.0) v. 3.5 (0.5 - 9.0); $p<0.001$).^[26]

Education

In Pennsylvania, USA, an inner-city home-based asthma education and environmental remediation programme that addressed both indoor and outdoor triggers through collaboration between a health system and a local environmental justice organisation showed some improvement, although not statistically significant, in pre- and post-test ACT scores in children with asthma.^[27] For the children who began with a c-ACT or ACT score <20 , there was significant improvement from pre-test to post-test (c-ACT $p<0.001$, ACT $p=0.050$) and a mean difference of 3 and 4 points, respectively.

A small RCT in Korea, with 30 participants, assessed different modes of education on asthma control status. Immersive virtual reality (VR) education involved sitting in front of a computer using an Oculus Rift DK2 head-mounted display system (Facebook Technologies, LLC, USA) set to an environmental education programme.^[28] The control group received a verbal explanation from an asthma medical professional for the same amount of time, together with printed material used for environmental management education for asthma patients in the clinic. The education time was 15 minutes for both the VR and the control groups. There was no significant difference between the ACT scores in the two study arms before and after the programme ($p>0.05$).^[28]

Risk of bias

Most of the studies reviewed have a high risk of bias as a result of the study methodology (Table 3). There was no randomisation in six of the eight studies. In some studies, there was lack of clarity on participant recruitment, selection and allocation. The outcomes measured could have been influenced by multiple confounders. A meta-analysis could not be completed owing to heterogeneity in methodology and multiple outcomes measured.

Discussion

In this systematic review, we identified multiple interventions to improve air quality and their outcomes, including the effect on asthma. Of the eight eligible studies, with a total of 11 395 043 participants, only two were RCTs. Interventions included population-level interventions such as air quality alerts, which showed improvement in asthma control and ED visits. Use of mobile technology applications with alerts also resulted in modest improvements in asthma control, but not in lung function. Additionally, air pollution reduction measures such as a clean air policy improved air quality, but disappointingly did not meaningfully improve lung function.

Air quality alerts are reported to be more effective when combined with behavioural changes following high alert notification. The US Environmental Protection Agency's Smoke Sense app has been widely used, but self-selected users responded to symptoms rather than preventing symptoms via risk reduction.^[29] Globally, air quality alert programmes represent one of the most common public responses to protect the population from air pollution.^[22] However, few studies have measured the effectiveness of mobile applications on objective

measures of wildfire smoke risk reduction or asthma-related clinical outcomes.^[29,30] The app myAirCoach demonstrated effectiveness in improving asthma control but not lung function at 6 months.^[30] Alert announcements reduced asthma-related ED visits by 25% in one study, and these air quality assessments can be done via online services as well.^[21,31]

The COVID-19 lockdown was associated with significantly reduced air pollution

globally. Air pollution emission reduction policy implementation showed reduced asthma exacerbations requiring ED visits, improved asthma control and fewer asthma-related admissions. Reductions in transportation sector emissions are largely responsible for the nitrogen dioxide anomalies.^[32] Pollution in some of the epicentres of COVID-19, such as Wuhan, Italy, Spain, the USA and Brazil, decreased by

up to 30%.^[33] The lockdown in Yichang was associated with a decrease in hospital and outpatient visits for asthma.^[34] Many countries reported that hospitalisations due to asthma decreased substantially during the pandemic. It is not clear whether the decreases were due to a reduction in symptoms, reluctance to visit hospitals, or reduced exposure to viral infections. Lockdown with social distancing measures was the major measure to mitigate cross-infection and spread of COVID-19.^[35-37] Benefits have also been observed following local air quality interventions associated with factory closures. Hospital admissions for childhood asthma fell by half, in association with a significant reduction in PM2.5, as a result of a 13-month closure of a steel mill in Utah Valley.^[38]

Reduction in air pollution can also be achieved through adopting clean, efficient and expanded public transport systems coupled with car share/club schemes and as much active transport in the form of walking and safe cycling as is feasibly possible.^[11] Decreases in ambient nitrogen dioxide and PM2.5 between 1993 and 2014 in one study were associated with a decreased asthma incidence.^[39] One of the studies in this review showed that adoption of ultra-low-sulphur diesel was associated with improvements in lung function, but this was not statistically significant with wide CIs and could not be distinguished from no association.^[23]

Vehicle electrification has substantial potential to reduce climate change damage and air pollution damage.^[40] Data from many parts of the world strongly suggest that policies designed to reduce air pollution can improve respiratory outcomes.^[11] Deciding upon and executing the necessary policies is a complex challenge when it necessitates, among other measures, a reduction in road traffic and a cleaner and greener element to what remains on the road – coupled with a heavy burden of expenditure. Policymakers are invariably torn between tightening controls on emissions to enhance health and succumbing to economic pressures not to reduce emissions.^[11]

The National Asthma Education and Prevention Program in the USA recommends that disparate groups receive culturally competent clinical asthma management and patient education, and recommends community-based interventions to include education and remediation of pollutants

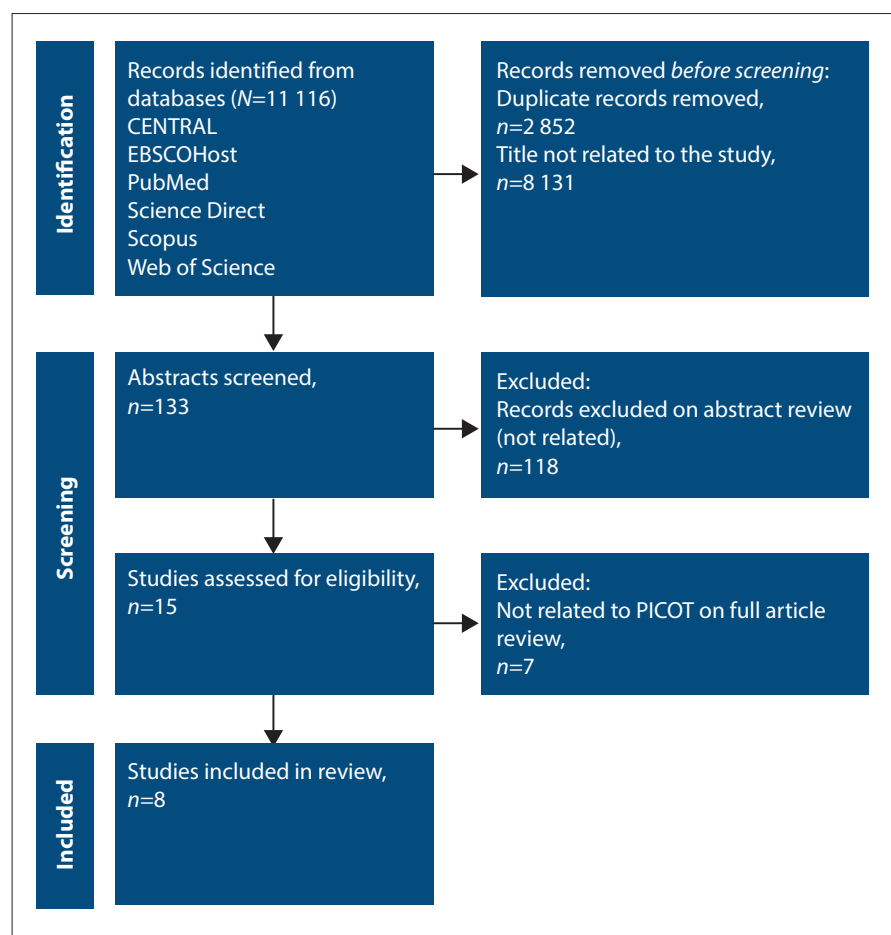


Fig. 1. Study eligibility chart according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. (PICOT = Population, Intervention, Comparator, Outcome, Time.)

Table 1. PICOT search criteria

	Studies with participants who have asthma and exposure to outdoor air pollution
Population	Participants of any age, any gender, and any asthma severity
Intervention	Any form of outdoor air pollution reduction strategies
Comparator	No interventions done to reduce exposure to outdoor air pollution
Outcome	The primary outcome measure was asthma outcomes such as symptom control as measured by the ACT or c-ACT; asthma exacerbations, and lung function as assessed by FEV ₁ , FVC and ratio of FEV ₁ to FVC
Time	Studies published between April 2012 and March 2022

PICOT = Population, Intervention, Comparator, Outcome, Time; ACT = Asthma Control Test; c-ACT = Childhood Asthma Control Test; FEV₁ = forced expiratory volume in the 1st second; FVC = forced vital capacity.

Table 2. Characteristics of interventions

First author and year	Study design	Country	Total participants, N	Age (years)	Intervention	Comparator	Outcome measured	Results	Study period/follow-up
Chen, 2018 ^[21]	Regression discontinuity study design	Canada, Toronto	All individuals who resided in the city of Toronto (Ontario) from 2003 to 2012 2.6 million	All ages	Air quality alert programme	Pre-programme	Asthma-related ED visits	Alert announcements reduced asthma-related ED visits by 4.7 per 1 000 000 people per day (95% CI 0.55 - 9.38), or 25% (95% CI 1 - 47).	One year (143 days fell within 5 units around the AQI threshold). Of these, 41 days were above the threshold (AQI ≥48) and therefore classified as eligible for alerts (eligible days). 8 weeks
Postma, 2021 ^[22]	RCT	USA, Washington State	n=67 n=22 controls n=22 SSU n=23 SSU-P	18 - 26	SSU SSU-P	No intervention	ACT and FEV ₁	Increased ACT and decreased predicted FEV ₁ from baseline in the intervention group. Increased ACT and no difference in predicted FEV ₁ from baseline in the control group.	8 weeks
Adar, 2015 ^[23]	Cohort	USA, Washington State	275 n=126 no asthma n=126 intermittent asthma n=23 persistent asthma	6 - 12	Adoption of clean air technology and fuel	Pre-policy adoption	AP reduction and improved lung health	PM2.5 and FENO levels were reduced. Changes in FVC and FEV ₁ (0.02 (95% CI 0.003 - 0.05) and 0.01 (95% CI -0.006 - 0.03) L/yr, respectively) were insignificant. Lower absenteeism (8% reduction (95% CI -16 - -1) with ULSD.	4 years
Kim, 2019 ^[24]	Cohort	Korea, Seoul and Daejeon	Seoul 8 789 984 Daejeon 1 466 172	0 - ≥65	Implementation of AP emission reduction policies Population from metropolitan city	Daejeon compared with Seoul	Hospital visits for asthma Air pollution reduction	Prevented hospital visits cases for asthma in Seoul in the total population and younger population (0 - 18 years) were estimated as 500 000 (11.3% of hospital visit cases if there was no intervention) cases and 320 000 (15.5% of hospital visit cases if there was no intervention) cases, respectively. 50% reported better symptoms, 38% less use of bronchodilators, ACT ≥20 improved post lockdown from 41.1% to 60.7% (p=0.001). Levels of CO, SO ₂ and NO ₂ were decreased.	9 years 2003 - 2007 pre-policies 2008 - 2011 post implementation
Ayaz, 2021 ^[25]	Cohort	Saudi Arabia, Riyadh	56	22 - 61	Lockdown	Pre-lockdown	Asthma control	50% reported better symptoms, 38% less use of bronchodilators, ACT ≥20 improved post lockdown from 41.1% to 60.7% (p=0.001). Levels of CO, SO ₂ and NO ₂ were decreased.	12-week lockdown

continued

Table 2. (continued) Characteristics of interventions

First author and year	Study design	Country	Total participants, N	Age (years)	Intervention	Comparator	Outcome measured	Results	Study period/follow-up
Kelly, 2022 ^[26]	Cohort	Ireland, Dublin	4 551 admissions n=3 573 pre n=978 post	Mean (SD) 40.9 (20.3)	Lockdown	Pre-lockdown	Change in air pollution levels and asthma admissions	Both PM2.5 and NO2 (p=0.002 and p<0.001, respectively) were decreased. Daily asthma admissions (mean (SD)) decreased from 4.5 (3.4) to 2.8 (2.5) (p<0.001).	802 days pre-pandemic and 353 days during pandemic
Shani, 2015 ^[27]	Pre- and post test	USA, Pennsylvania	80 children	2 - 17	Education about AP triggers	Pre-intervention	Reduce exacerbation and improve asthma control	Reduction in emergency room visits, decreases in school absenteeism and use of rescue medications.	6 months
Kim, 2022 ^[28]	RCT	Korea	30 n=15 in each group	Mean (SD) 12 (2.6)	Immersive VR education	Control	ACT c-ACT	No significant improvement in ACT scores before and 4 weeks after training.	4 weeks

ED = emergency department; CI = confidence interval; AQI = Air Quality Index; RCT = randomised controlled trial; Smoke Sense Urbanova smartphone; SSU-P = SSU Plus smartphone; ACT = Asthma Control Test; FEV₁ = forced expiratory volume in 1st second; AP = air pollution; PM2.5 = particulate matter ≤2.5 microns in diameter; FENO = fraction of exhaled nitric oxide; FVC = forced vital capacity; CO = carbon monoxide; SO₂ = sulphur dioxide; NO₂ = nitrogen dioxide; SD = standard deviation; VR = virtual reality; c-ACT = Childhood Asthma Control Test.

in the indoor environment and outdoor air.^[41] The studies on the impact of education on asthma control report conflicting results.^[27,28] In one study, addition of the Air Quality Index to asthma action plans led to improved asthma control as shown by ACT scores.^[42]

The strength of this systematic review lies in the broad search, which was also not limited by age or countries' income status. Limitations include that a meta-analysis was not possible owing to the small number of studies and the heterogeneity of studies, and that a funnel plot to compare the precision and the results of the studies was not possible. Most studies were at high risk of confounding and bias.

Conclusion

Air pollution is a major hazard, and strategies to reduce exposure have positive outcomes in terms of the asthma burden. Implementation of global measures that aim to reduce exposure to air pollutants, such as air pollution reduction policy implementation, education, air quality alerts and behavioural change, is recommended to improve asthma (and wider health) outcomes. We found some evidence that outdoor air pollution reduction interventions had beneficial effects on asthma control. This field would benefit from further high-quality RCT evidence to inform policy and decision-making.

Recommendations

A wider range in terms of time frame is recommended to widen the search pool. We recommend inclusion of both indoor and outdoor air pollution exposure in the hope of yielding a better result in determining the burden of air pollution and its impact on asthma. The findings of the present review indicate that focusing of education together with behavioural changes can reduce exposure at the individual level. The implementation of clean air policies reduces air pollution exposure and as a result improves lung health.

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Table 3. Risk-of-bias assessment of air pollution reduction intervention studies in patients with asthma

First author and year	Outcome	D1	D2	D3	D4	D5	Overall
Kim, 2022 ^[28]	Asthma control status	+	+	+	+	+	+
Ayaz, 2021 ^[25]	Asthma control	-	+	+	+	+	-
Postma, 2021 ^[22]	ACT and FEV ₁	+	+	+	+	+	+
Shani, 2015 ^[27]	Reduction in exacerbations and improved asthma control	-	+	+	+	+	-
Kelly, 2022 ^[26]	Asthma admissions	-	+	+	+	+	-
Adar, 2015 ^[23]	Improved lung health	-	+	+	+	-	-
Chen, 2018 ^[21]	Asthma-related emergency visits	-	-	+	+	-	-
Kim, 2019 ^[24]	Hospital visits for asthma	-	+	+	+	+	-

D1 = randomisation process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result; + = low risk; - = high risk; ACT = Asthma Control Test; FEV1 = forced expiratory volume in 1st second.

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