

BMJ Open Associations between environmental exposures and asthma control and exacerbations in young children: a systematic review

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ABSTRACT

Objective: To complete a systematic review of the literature describing associations between all environmental exposures and asthma symptoms and exacerbations in children up to mean age of 9 years.

Design: Systematic review.

Setting: Reference lists of identified studies and reviews were searched for all articles published until November 2013 in electronic databases (MEDLINE, EMBASE, CINAHL, Cochrane Controls Trials Register).

Participants: Studies were selected which examined a link between exposure to environmental factors and asthma symptoms and exacerbations where the study participants were children with a mean age of ≤ 9 years.

Primary and secondary outcome measures:

Indices of asthma symptoms, control and exacerbations.

Results: A total of 27 studies were identified including eight where inhaled allergens and four where environmental tobacco smoke (ETS) were the exposures of interest. There was evidence that exposure to allergen, ETS, poor air quality and unflued heaters had a modest magnitude of effect (ORs between 2 and 3). There was also evidence of interactions observed between exposures such as allergen and ETS.

Conclusions: Exposure to inhaled allergens, ETS, unflued heaters and poor air quality has an important effect on exacerbations in young children with asthma and should be minimised or, ideally, avoided. Better understanding of the effect of exposure to damp housing, air conditioning and dietary factors plus interactions between environmental exposures associated with exacerbations is required.

INTRODUCTION

Childhood asthma is a chronic respiratory condition characterised by episodic symptoms of cough, wheeze and shortness of breath.¹ There are approximately one million children with asthma in the UK,² and in England and Scotland between 50 and 100 children are admitted to hospital each day due to asthma.^{3 4} Although difficult to

Strengths and limitations of this study

- This is the first systematic review of the literature.
- The age range is up to mean age of 9 years.
- Only 27 studies were identified.

quantify,⁵ increased childhood asthma symptoms which are not considered an asthma exacerbation also yield a burden of morbidity due to missed exercise and education and cost due to increased medication use.

The mechanism(s) leading to poor control of asthma symptoms and ultimately asthma exacerbations is complex but environmental exposures are generally assumed to be important.^{6 7} In 2000, the US National Academy of Sciences Institute of Medicine concluded that across all ages, there was strong evidence for causal relationships between exposure to house dust mite allergen (HDM), environmental tobacco smoke (ETS), cat and cockroach allergen and asthma exacerbation.⁸ In addition, there was limited or sufficient evidence associating exposures to dog allergen, moulds and formaldehyde and asthma exacerbation.⁸

Despite the high burden of asthma symptoms in young children and the understanding that environmental exposures are important triggers for symptoms, we are not aware of a systematic review of the literature in this age group. In 2009, the Scottish Government commissioned the Environmental Determinants of Public Health in Scotland (EDPHiS) programme which was aimed at understanding (1) how environmental exposures of young people affect the prevalence and severity of four priority areas including asthma, obesity, unintentional injury and mental health and well-being and (2) what evidence there is from studies, internationally, of the success (or not) of interventions intended



to improve children's health via the environment. The objective of this systematic review was to capture the literature associating environmental exposures and childhood asthma symptoms (including exacerbations) in young children, that is, populations where the mean age was not more than 9 years. A second systematic review by our group will describe environmental factors associated with asthma causation.

METHODS

Developing search strategy

The EDPHiS programme was designed to quantify the evidence linking the environment and key aspects of health of young children (defined as mean age ≤ 9 years) in order to inform the development of public policy. A stakeholders' workshop was held to identify environmental influences on asthma, involving senior researchers from government and academia, health practitioners and policy professionals. The areas which emerged from this workshop were then refined and distilled by the study team to those as being of potential relevance to asthma exacerbation (box 1). Asthma aetiology was considered as a separate topic but the search strategy was designed to identify studies relating environmental exposures to asthma causation and asthma exacerbation.

Search strategy and data sources

The search strategy for MEDLINE is provided in the online supplementary material. Two reviewers (SD and ED) searched the electronic databases (including MEDLINE, EMBASE, Cochrane controlled trials register and CINAHL) and reference lists of other studies and reviews. Electronic and manual searching were carried out between January 2010 and April 2010 and updated searches for articles were carried out in July 2011 and November 2013. No date limits were applied to the search strategy. Studies identified from searching electronic databases were combined, duplicates removed

Box 1 Areas for environmental determinants of exacerbation of asthma, as derived from stakeholder workshops

Environmental tobacco smoke (antenatal and postnatal)
 Outdoor air quality (including traffic fumes, volatile organic compounds (VOC's), chlorine, phthalates, sulfur dioxide and ozone)
 Damp housing/ mould
 Inhaled allergens (house dust mite, pets and pollens)
 Domestic combustion (gas, solid fuel and candles)
 Industrial combustion (incinerators)
 Air conditioning and humidifiers
 Dietary exposures (maternal diet, breastfeeding and diet in childhood)
 Respiratory virus infection
 Fireworks and bonfires
 Vacuuming

and papers were screened for relevance to the review based on the information contained in the title and abstract.

Inclusion/exclusion criteria

Studies were then considered by a second reviewer (ST) and included if (1) the mean age of the participants was ≤ 9 years, (2) they captured exposure to an environmental factor identified as potentially relevant to asthma exacerbation and/or symptoms (3) comparisons made within a population of children with asthma; (4) outcomes included diagnosis of asthma or data related to healthcare utilisation (hospital admissions and drug use) and morbidity and functional status, lung function tests, measures of self-perception of health status (symptom free days) and well-being and quality of life; (5) the study design was either a meta-analysis, systematic review, randomised control trials (RCTs), non-RCTs or cohort studies. If no evidence was apparent for an exposure, then studies meeting the lower Scottish Intercollegiate Guidelines Network criteria were considered, that is, cross-sectional studies (including panel studies), case-control and case report studies.⁹ Clinical trials of medications were excluded.

Study selection and data collection

The full text of references identified as potentially relevant were obtained: papers that could not be rejected with certainty were assessed independently by another reviewer (ST) using the inclusion criteria. Differences were resolved by discussion and consensus between reviewers (SD and ST). Data were extracted regarding study design, sample size, participants, aim, intervention and outcomes/results by one reviewer (SD) into a table format (see online supplementary material). Each study was summarised and described with regard to characteristics of participants, aim, characteristics of interventions and key results.

Quality assessment

Quality assessment of all the included papers was carried out using 'Effective public health practice project quality assessment tool for quantitative studies' (<http://www.ephp.ca/Tools.html> accessed January 2013). The tool was modified to take into account the design of the included studies.

RESULTS

Literature search

There were 14 691 references identified from electronic databases and other studies. Initial screening produced 129 potentially relevant references and 28 studies met the inclusion criteria after further screening of full-text articles. One study was removed since the analysis excluded children with asthma.¹⁰ Search results are summarised in the QUORUM flow diagram (figure 1). There was 1 systematic review, 11 cohort studies, 10

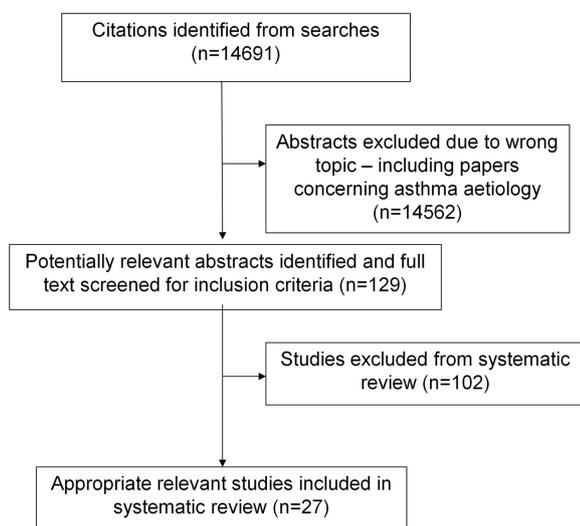


Figure 1 QUOROM flow chart.

intervention studies, 4 cross-sectional studies and 1 case-control study. There were 16 studies from North America, 5 studies from Europe (including the systematic review), 2 from Japan and 1 each from Australia, New Zealand, Hong Kong and Egypt. All but one of the studies was published after 2000. The online supplementary table 1 shows characteristics of the included studies. No studies were identified for exposure to emissions from industrial sources or maternal diet, fireworks and bonfires or vacuuming. Results of the quality control are presented in the online supplementary material; there were 2 papers with a strong global rating, 20 with a moderate rating and 6 rated as weak.

Environmental tobacco smoke

One longitudinal¹¹ and three cross-sectional studies^{12–14} were identified. The longitudinal study¹¹ measured exposure to ETS in 1444 children with asthma and NO₂ in a subset of 663, and follow-up over 9 months revealed increased symptoms in those with higher exposure to NO₂ but only among non-atopic children (relative risk 1.8 (95% CI 1.1 to 2.8)). There was no association between symptoms and higher ETS exposure. One cross-sectional study (which was given a weak global rating) recruited 282 children with physician-diagnosed asthma and categorised them as having no, mild or heavy ETS exposure.¹² The children with no and mild ETS exposure had similar symptom scores but compared with those with heavy ETS exposure had lower scores (2.3 for no and mild exposure combined vs 2.8 p=0.0048) and were at reduced risk for requiring treatment with long-acting β agonist (24% vs 43% p=0.035) and leukotriene receptor antagonist (74% vs 95% p=0.0002) compared with those with high exposure. Exacerbations were not reported. A second cross-sectional study from the USA¹³ recruited 590 young children with at least one of three features of asthma (ie, physician diagnosed asthma, symptoms suggestive of asthma or emergency department presentation

with asthma) and categorised those exposed to ETS as low (n=82) or moderate/high (n=71) exposure groups; the moderate/high group were at an increased risk for mild persistent nocturnal symptoms (OR 3.4 (95% CI 1.3 to 8.8)) and moderate-to-severe nocturnal symptoms (OR 2.3 (95% CI 1.0 to 5.1)) compared with the low exposure group. There was a trend for the moderate-to-high exposure group to have limited physical activity compared with the low exposure group (OR 1.8 (95% CI 0.9 to 3.5)). An earlier study from the USA¹⁴ (which was given a weak global rating) recruited 199 children with asthma of whom 53 lived with only one adult who smoked and 30 lived with two adults who smoked; the risk for an exacerbation over the past 12 months was 1.8 (95% CI 1.4 to 2.2) for those living with two compared with one adult who smoked.

Air quality

There were six papers from five longitudinal studies^{15–20} and one cross-sectional study²¹ identified. In one longitudinal study,¹⁵ outdoor concentrations of PM_{2.5}, NO₂, sulfur dioxide (SO₂), carbon monoxide (CO) and ozone (O₃) were related to daily spirometry and symptoms over 1 year in 861 atopic children with persistent asthma; in a one-pollutant model, only PM_{2.5}, NO₂ and SO₂ were related to outcomes. In a three-pollutant model (including PM_{2.5}, NO₂, SO₂), higher exposure to NO₂ was associated with increased risk for cough and wheeze (OR 1.2 (95% CI 1.0 to 1.5)) and increased exposure to NO₂ and PM_{2.5} were associated with mean reductions in forced expiratory volume in 1 s (FEV₁) between 0.5% and 1% predicted. A second longitudinal study of 846 children with physician-diagnosed asthma or recent symptoms consistent with asthma observed each quartile of increased ozone exposure were associated with an increased risk of morning asthma symptoms over 4 months (OR 1.16 (95% CI 1.02 to 1.30)) and a 59% decline in peak expiratory flow (95% CI 0.13 to 1.05).¹⁶ Increased morning symptoms were also associated with quartile increase in SO₂ (OR 1.32 (95% CI 1.03 to 1.70)), NO₂ (OR 1.48 (95% CI 1.02 to 2.16)) and PM₁₀ (OR 1.26 (95% CI 1.0 to 1.59)). Multipollutant models were not applied so the more specific role of each pollutant could not be ascertained. In a cohort study¹⁷ the risk of presentation to hospital for acute asthma was higher among those with exposure to high concentrations of ozone (>70 ppb; OR for admission per quartile increase in ozone 1.68 (95% CI 1.64 to 1.73)). A further longitudinal study-related exposures to PM_{2.5–10} and PM_{2.5} in the bedrooms of 150 young children with asthma or asthma-related symptoms over 6 months¹⁸: each 10 $\mu\text{g}/\text{m}^3$ increase in exposure to PM_{2.5–10} was associated with a mean 6% rise in symptoms (95% CI 1 to 12) and a similar rise in PM_{2.5} was linked to a mean rise of 3% which approached significance (95% CI –1 to 7). A second publication¹⁹ from the previously mentioned cohort¹⁸ found similar positive associations between PM exposures and symptoms in atopic and non-

atopic children. A final longitudinal study²⁰ measured NO₂ exposure, asthma symptoms and indoor allergen exposures at 1-month intervals over a year. Independent of allergen exposures and compared with the lowest two quintile for NO₂ exposure, the highest two quintiles of exposure were at increased risk for asthma symptoms, reliever medication use and had more severe asthma, for example, the ORs for wheeze and reliever medication use in the highest quintile were 1.5 (95% CI 1.1 to 2.0) and 1.7 (1.3 to 2.3), respectively.²⁰ The rationale for this longitudinal study²⁰ came from an earlier cross-sectional study²¹ by the same group who recruited 728 children with asthma and related symptoms to exposure to indoor NO₂ (presumed to originate from gas stoves) over the previous month. Each 20 ppb rise in NO₂ was associated with increased wheeze (OR 1.5 (1.0 to 2.2)) and chest tightness (OR 1.6 (1.0 to 2.5)).²¹

Damp housing/mould

In the intervention study identified,²² where children were recruited after presenting to primary or secondary care with acute asthma symptoms, there was a reduction in exacerbations in the intervention group compared with the control group (10% vs 28%, absolute numbers of exacerbations 1 vs 11) However, the study had a small sample size (n=62) and the ages of the children ranged from 2 to 17 years. In an observational study, indoor and outdoor air samples for fungi were obtained on five occasions over 2 years from the homes of 936 children with moderate-to-severe asthma. Exposure to fungal species was associated with increased asthma exacerbations among children exposed to those species compared with non-sensitised peers²³; typically, the increased risk for exacerbation was 1.4 per 10-fold increase in outdoor or indoor fungal exposure.

Inhaled allergens

There were six intervention studies^{24–29} (including one where all participants received the intervention²⁹) and two cohort studies.^{30–31} One intervention study where 20 children with asthma being followed up in secondary care and with high plasma HDM-IgE concentrations were randomised to HDM-free pillows or 'placebo' pillows with HDM-permeable fabric²⁴ demonstrated that intervention was associated with a reduction in HDM exposure and HDM-IgE levels but not in symptoms over 12 months. A second study randomised 60 HDM-sensitised children with physician-diagnosed asthma to HDM-free mattress and pillow encasings²⁵; over 1 year the intervention group had a reduced exposure to HDM allergen and were more likely to have had halved their dose of inhaled steroids when compared with the control group (73% vs 24%, p<0.001), the reduction in ICS did not occur until 6 months after the intervention was made. There was no overall reduction in symptom score between the two groups. In a third study (which was given a weak global rating), asthma severity scores did not differ between groups who were recruited following an admission with

asthma and who received either environmental and educational intervention or standard care²⁶; the intervention included dust mite impermeable mattress and bedding covers, professional house cleaning and cockroach bait placed in the house. A study that was given a strong global rating, where 937 children aged 5–11 years with physician-diagnosed asthma were randomised to an intervention aimed at reducing exposure to HDM and cockroach plus some environmental education found greater reductions in HDM exposure among the intervention group over the 14-month follow-up.²⁷ The intervention group had significantly fewer days with symptoms compared with the control group during the intervention year (3.39 vs 4.20 days, p<0.001) and in the follow-up year (2.62 vs 3.21 days, p<0.001). The reduction in symptoms was proportionate to the reduction in exposure to HDM and other allergens. A small intervention study randomised a total of 160 HDM-sensitised children with asthma to either chemical, physical or both interventions or control and reported that children in the three intervention arms all had improvements of 2% predicted FEV₁ compared with control.²⁸ A final intervention study, where there was no control arm and which was given a weak global rating and all 243 individuals were given a comprehensive allergen and educational intervention, found improved symptoms 6 months after intervention compared with baseline.²⁹ One cohort study related grass pollen exposures to symptoms and rescue medication use in 430 children with asthma and reported associations among the subgroup of children in receipt of maintenance treatment and sensitised to grass.³⁰ The greatest increase in symptoms (OR 2.4 (95% CI 1.5 to 3.7)) and rescue medication use (OR 1.2 (95% CI 1.0 to 1.4)) was seen among those in the second highest compared with the lowest quintile. A second cohort study of 181 1–4-year-olds with asthma (defined as ≥3 episodes of wheeze)³¹ reported that exposure to cat allergen in the first 2 years of life was associated with increased cat sensitisation at 4 years of age (OR 5.6 (95% CI 1.1 to 29.0)). Severe asthma (present in 12 individuals) was not more likely (OR 3.4 (0.8, 14.9)) among those with high cat allergen exposure (Fel d1), nor among those with exposure to ETS (OR 3.0 (95% CI 0.7 to 12.2)) but those few exposed to cat and ETS were more likely to have severe asthma (OR 18.0 (95% CI 3.2 to 101)).

Domestic combustion

One RCT, which was given a strong global rating, involving 409 children with doctor-diagnosed asthma and symptoms in the past years used non-polluting more effective home heaters (either wood pellet burners, heat pumps or flued gas heaters) during winter.³² The intervention group had fewer days off school (mean difference 1.8 (95% CI 0.1 to 3.1)), fewer visits to the doctor (mean reduction 0.4 (95% CI 0.1 to 0.6)) and fewer reports of poor health (OR 0.5 (95% CI 0.3 to 0.7)). There was no change in the lung function. A second RCT, which was given a weak global rating, where unflued gas classroom heaters were replaced over winter

with either gas flued or electric heaters found that intervention was associated with improved asthma control among children with physician-diagnosed asthma including reduced difficulty in breathing by day (RR 0.4 (95% CI 0.1 to 1.0)) and by night (RR 0.3 (95% CI 0.1 to 0.7)) and in daytime asthma attacks (RR 0.4 (95% CI 0.2 to 0.9)).³³

Air conditioning and humidifiers

There was one systematic review³⁴ based on one RCT³⁵ of 40 HDM-sensitised adults and 27 children (mean age 9.7 years) attending asthma clinics. This study was included in the absence of any other data in young children. Groups of 10 individuals were randomised to either mechanical ventilation with heat recovery (MVHR) in bedrooms and bathrooms and/or a high-efficiency vacuum cleaner or neither. The intervention with MVHR (with and without the vacuum cleaner) significantly reduced humidity and HDM numbers and concentrations in bedroom carpet exposure but did not result in any improvement in symptoms.

Dietary exposures

Allergens in diet

In a non-randomised pilot study, 22 children with physician-diagnosed mild or moderate asthma were given the option of avoiding egg, milk and related products for 8 weeks.³⁶ The intervention was associated with reductions in milk-specific and egg-specific IgE and a 22% increase in peak expiratory flow but with no change in symptoms in comparison with the control group.

Respiratory virus infections

A case-control study explored modifiable risk factors for asthma exacerbations in 168 children with asthma who were and were not admitted to hospital.³⁷ Cases who were hospitalised were more likely to have virus identified in nasal secretions (OR 5.4 (95% CI 2.1 to 14.0)) and to be exposed to an allergen to which they were sensitised (OR 2.9 (95% CI 1.5 to 5.6)) compared with those with asthma and not hospitalised. Exposure to virus and to allergen to which the child was sensitised was associated with a substantially increased risk of hospitalisation (OR 19.4 (95% CI 3.7 to 101.5)). A community-based observational study made over 12–15 months in 114 children with mild-to-moderate asthma but with no severe exacerbations for a year managed to obtain nasal secretions in 54% of respiratory episodes during the follow-up and detected virus in only 37% of these³⁸; PCR (the gold standard) was used for detection of only some viruses.

DISCUSSION

This is the first systematic review of the literature describing associations between environmental exposures and asthma symptoms and/or exacerbations in children with

mean age 9 years or younger. Our first finding was of a relative poverty of data given the high prevalence of asthma exacerbations and poor asthma control in children; less than half of the studies included were intervention studies. Among the studies which were included there were often different outcomes reported and this made meta-analysis invalid. The second finding was consistency in the association between exacerbations and some exposures, for example, to secondhand smoke, allergen, unflued heaters and poor air quality. In the occupational setting, exposures associated with similar magnitude increases in risk for exacerbation such as we describe here would lead to the development of exposure standards; parents, healthcare workers and politicians need to be mindful of the relevance of indoor and outdoor air quality on respiratory well-being in young children.

There are a number of factors which should be considered when interpreting our findings. In addition to the limitations in the literature previously discussed, some of the studies included were of small populations^{22 24 25 34 36 39} and, therefore, were underpowered and at risk for reporting false positive or negative outcomes. A second limitation is that the larger intervention studies experienced dropout which might have changed the demographics of the study population and this may have implications for generalisation. Third, our age limit was up to mean age 9 years and our review will not have included papers describing the effect of exposures on older children. Fourth, there is no gold standard definition of asthma and although the majority of studies included applied physician-diagnosed asthma as the definition, the lack of an objective asthma definition will introduce heterogeneity between studies making direct comparison challenging. Finally, there are many other factors other than environmental exposure which are associated with poor asthma control and exacerbations and these include exercise, changes in the weather, emotions and stress and poor treatment compliance; what is not clear is the hierarchy of environmental exposures within this (not exhaustive) list of factors.

There was mostly consistent evidence linking exposure to inhaled allergen and ETS with increased risk of asthma symptoms, the magnitude of effect being approximately 2–3-fold although one study found an association between increased ETS exposure and reduced peak flow but not increased symptoms.¹¹ In addition, there was evidence that in some settings, indoor heating during winter was associated with a doubled risk for asthma symptoms and that changes in outdoor air quality have a positive linear effect on asthma symptoms. While exposures to ETS and allergens in isolation had a modest effect, in two studies,^{31 37} there was evidence of interactions between exposures with an apparently large effect on asthma symptoms. While it is tempting to hope that improved asthma control and reduced exacerbations for young children might be achieved by multifaceted, rather than



unifaceted interventions, for example, ETS and allergen reduction interventions, there were multifaceted interventions identified in this review which failed to improve asthma control^{26 34} although one study did achieve a reduction in symptoms and asthma control.²⁷ At this point in time, there is uncertainty in the literature as to whether multifaceted environmental interventions offer greater relief of symptoms in children with asthma compared with effective unifaceted interventions.

Many potentially harmful environmental exposures are correlated, for example, PM_{2.5}, NO₂ and fungal species, and some studies included in this review and also those excluded but worthy of mention gave an insight into this complexity. Two studies included in this review^{19 30} illustrate how NO₂, SO₂, CO, PM_{2.5} and O₃ concentrations are all correlated, but when considered together in one study,¹⁹ the effect of outdoor NO₂ exposures on asthma outcomes subsumed effect of other exposures; thus, associations with O₃ and asthma outcomes^{16 17} may not be causal. In a study of children where the mean age was 10 years and therefore not included in this review,⁴⁰ there was a positive correlation between PM_{2.5} exposure and reliever medication use but only when ETS exposure was low (ie, urinary cotinine/creatinine ratio <10 ng/mL/mg); at higher ETS exposures, reliever medication use was higher but there was no relationship with increasing PM_{2.5} exposure despite ETS being the primary source for indoor PM_{2.5}. This might suggest that there is a ceiling effect of exposure to PM_{2.5} on asthma symptoms but not for ETS exposure. A second study where mean age was 9.6 years⁴¹ and therefore not included compared the relationship between indoor and outdoor NO₂ exposures to symptoms and FEV₁. Indoor exposures were approximately 50% higher than outdoor exposures and only indoor exposures were linked to (slightly) increased symptoms and reduced lung function. The study by Pongracic *et al*²³ also demonstrated how indoor and outdoor fungal exposures are positively correlated and also how individual exposures within a composite exposure are correlated. To establish which single exposure is causally related to increased asthma symptoms requires very large study populations, particularly given the relatively small effect size, and whole (national) population studies may provide the basis for such work.

Unifaceted intervention studies designed to modify environmental exposure are challenging, often fail to modify exposure and even when successful, modification of a single exposure is often ineffective, for example, HDM.⁴² However, proof-of-concept that the environment can be modified to the benefit of children's asthma symptoms is seen following the introduction of smoking bans in the UK which were associated with reduced hospitalisation of children for asthma.^{3 4} What remains unknown is which environmental exposures can be modified and which modifications are effective. While we found little or no evidence linking exposure to ingested allergens, inhaled moulds, traffic fumes and

vacuuming to increased asthma symptoms, the absence of evidence is not evidence of absence and more research is required in these areas. Future interventions might consider the seasonality of asthma symptoms and exacerbations, typically September in northern hemisphere³ and interventions might be focused at certain times when exacerbations are known to occur.

In summary, this review finds evidence for a link between increased asthma symptoms and exacerbations and exposure to potentially modifiable environmental exposures. What is now required are intervention studies which effectively modify exposures such as secondhand smoke, allergen exposure, outdoor air quality and heaters in large study populations.

Contributors JGA, HC and ST were involved in conception and design. SD and ED undertook the analysis. SD drafted the initial version of the manuscript and all authors contributed to revisions. ST is the guarantor.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Fuller details of the papers included in this systematic review are available on the supplementary data file. No additional unpublished data are available.

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