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

Smita Dick,1 Emma Doust,2 Hilary Cowie,2 Jon G Ayres,3 Steve Turner1

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 quantify, 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

1Child Health, University of Aberdeen, Aberdeen, UK
2Institute of Occupational Medicine, Edinburgh, UK
3Institute of Occupational and Environmental Medicine, University of Birmingham, Birmingham, UK

Correspondence to
Dr Steve Turner;
s.w.turner@abdn.ac.uk
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 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.ephpp.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

---

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 (VOCs), 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
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 longitudinal study and three cross-sectional studies were identified. The longitudinal study 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 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 USA (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 and one cross-sectional study identified. In one longitudinal study, outdoor concentrations of PM2.5, 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 PM2.5, NO2 and SO2 were related to outcomes. In a three-pollutant model (including PM2.5, 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 PM2.5 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). 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 study, 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 PM2.5–10 and PM2.5 in the bedrooms of 150 young children with asthma or asthma-related symptoms over 6 months; each 10 µg/m3 increase in exposure to PM2.5–10 was associated with a mean 6% rise in symptoms (95% CI 1 to 12) and a similar rise in PM2.5 was linked to a mean rise of 3% which approached significance (95% CI −1 to 7). A second publication from the previously mentioned cohort found similar positive associations between PM exposures and symptoms in atopic and non-
atopic children. A final longitudinal study 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 quintiles 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. The rationale for this longitudinal study came from an earlier cross-sectional study 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)).

**Damp housing/mould**

In the intervention study identified, 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 in exacerbations in the intervention group compared with control). A second cohort study of 181 1–4-year-olds with asthma (defined as ≥3 episodes of wheeze) 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 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 and who received either environmental and educational intervention or standard care, 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. 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. A final intervention study, where there was no control arm and which was given a weak global rating, where 243 individuals were given a comprehensive allergen and educational intervention, found improved symptoms 6 months after intervention compared with baseline. 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. 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) 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)).

**Inhaled allergens**

There were six intervention studies (including one where all participants received the intervention) and two cohort studies. 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 fabric 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 encasings; 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 care, 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. 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. A final intervention study, where there was no control arm and which was given a weak global rating, where 243 individuals were given a comprehensive allergen and educational intervention, found improved symptoms 6 months after intervention compared with baseline. 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. 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) 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. 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)).

**Air conditioning and humidifiers**

There was one systematic review based on one RCT 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. 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. 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 12–18 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 these; 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 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. 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 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 although one study did achieve a reduction in symptoms and asthma control. 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$_{2.5}$, NO$_2$ 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 illustrate how NO$_2$, SO$_2$, CO, PM$_{2.5}$ and O$_3$ concentrations are all correlated, but when considered together in one study, the effect of outdoor NO$_2$ exposures on asthma outcomes subsumed effect of other exposures; thus, associations with O$_3$ and asthma outcomes may not be causal. In a study of children where the mean age was 10 years and therefore not included in this review, 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 years and therefore not included compared the relationship between indoor and outdoor NO$_2$ exposures to symptoms and FEV$_1$. 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 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. 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. 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 hemisphere 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.

**Funding** This study was funded by Good Places better Health Initiative of the Scottish Government, grant number EV028 RGC 1880.

**Competing interests** None.

**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.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

**REFERENCES**

1. British Thoracic Society and Scottish Intercollegiate Guidelines Network. Guideline 101: British Guideline on the Management of Asthma 2011. http://www.sign.ac.uk/guidelines/fulltext/101/index.html (accessed 04 Jan 2013).
2. Asthma UK. http://www.asthma.org.uk/about-asthma/my-child-has-asthma/asthma-your-child/ (accessed 28 Feb 2013).
3. Millett C, Lee J, Laverty AA, et al. Hospital admissions for childhood asthma after smoke-free legislation in England. Pediatrics 2013;131:e695–501.
4. Mackay D, Haw S, Ayres JG, et al. Smoke-free legislation and hospitalizations for childhood asthma. N Engl J Med 2011;363:1139–45.
5. Senhouser FH, Braun-Fahrlander C, Wildhaber JH. The burden of asthma in children: a European perspective. Paediatr Respir Rev 2005;6:2–7.
6. Etzel RA. How environmental exposures influence the development and exacerbation of asthma. Pediatrics 2003;112:233–9.
7. Jackson DJ, Sykes A, Mallick P, et al. Asthma exacerbations: origin, effect, and prevention. J Allergy Clin Immunol 2011;128:1165–74.
8. Institute of Medicine. Executive summary. Clearing the air: asthma and indoor air exposures. ed, 2000:1–18. http://books.nap.edu/openbook.php?record_id=9610&page=6.
9. Scottish Intercollegiate Guidelines Network. http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html (accessed 31 Jan 2013).
10. Melia RJ, Florey CD, Altman DG, et al. Association between gas nitric oxide and passive smoking on urban asthmatic children. J Allergy Clin Immunol 2007;120:618–24.
11. Kattan M, Gergen PJ, Eggleston P, et al. Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children. J Allergy Clin Immunol 2007;120:618–24.
12. Yamasaki A, Hanaki K, Tomita K, et al. Environmental tobacco smoke and its effect on the symptoms and medication in children with asthma. Int J Environ Health Res 2009;19:97–108.
13. Morkjærsonpang V, Rand CS, Butz AM, et al. Environmental tobacco smoke exposure and nocturnal symptoms among inner-city children with asthma. J Allergy Clin Immunol 2002;110:147–53.
14. Chilomczyk BA, Salmen LM, Megathlin KN, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *N Engl J Med* 1995;332:1657–62.

15. O’Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;121:1133–9.

16. Mortimer KM, Neas LM, Dockery DW, et al. The effect of air pollution on inner-city children with asthma. *Eur Respir J* 2002;19:699–705.

17. Lin S, Liu X, Le LH, et al. Chronic exposure to ambient ozone and asthma hospital admissions among children. *Environ Health Perspect* 2008;116:1725–30.

18. McCormack MC, Breysse PN, Matsui EC, et al. In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect* 2009;117:294–8.

19. McCormack MC, Breysse PN, Matsui EC, et al. Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma Immunol* 2011;106:308–16.

20. Belanger K, Holford TR, Gent JF, et al. Household levels of nitrogen dioxide and pediatric asthma severity. *Epidemiology* 2013;24:320–30.

21. Belanger K, Gent JF, Triche EW, et al. Association of indoor nitrogen dioxide exposure with respiratory symptoms in children with asthma. *Am J Respir Crit Care Med* 2006;173:297–303.

22. Kercsmar CM, Dearborn DG, Schluchter M, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environ Health Perspect* 2006;114:1574–80.

23. Pongracic JA, O’Connor GT, Mullenberg ML, et al. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. *J Allergy Clin Immunol* 2010;125:593–9.

24. Nambu M, Shirai H, Sakaguchi M, et al. Effect of house dust mite-free pillow on clinical course of asthma and IgE level—a randomized, double-blind, controlled study. *Paediatr Allergy Immunol* 2008;21:137–44.

25. Hakken S, Host A, Niklasson U, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol* 2003;111:169–76.

26. Williams SG, Boswell CM, Falter KH, et al. Does a multifaceted environmental intervention alter the impact of asthma on inner-city children? *J Natl Med Assoc* 2006;98:249–60.

27. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351:1088–90.

28. El-Ghitany EM, Abd El-Salam MM. Environmental intervention for house dust mite control in childhood bronchial asthma. *Environ Health Prev Med* 2012;17:377–84.

29. Largo TW, Borgiaiali M, Wisinski CL, et al. Healthy Homes University: a home-based environmental intervention and education program for families with pediatric asthma in Michigan. *Public Health Rep* 2011;126(Suppl 1):1350–7.

30. DellaValle CT, Triche EW, Leaderer BP, et al. Effects of ambient pollen concentrations on frequency and severity of asthma symptoms among asthmatic children. *Epidemiology* 2012;23:55–63.

31. Melen E, Wickman M, Nordvall SL, et al. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. *Allergy* 2001;56:646–52.

32. Howden-Chapman P, Pierse N, Nicholls S, et al. Effects of improved home heating on asthma in community dwelling children: a randomised controlled trial. *BMJ* 2008;337:a1411.

33. Pilotto LS, Nitschke M, Smith BJ, et al. Randomized controlled trial of unfurred gas heater replacement on respiratory health of asthmatic schoolchildren. *Int J Epidemiol* 2004;33:208–14.

34. Singh M, Bara A, Gibson P. Humidity control for chronic asthma. *Cochrane Database Syst Rev* 2002:2:CD003563.

35. Warner JA, Frederick JM, Bryant TN, et al. Mechanical ventilation and high-efficiency vacuum cleaning: a combined strategy of mite and mite allergen reduction in the control of mite-sensitive asthma. *J Allergy Clin Immunol* 2000;105:75–82.

36. Yusoff NA, Hampton SM, Dickerson JW, et al. The effects of exclusion of dietary egg and milk in the management of asthmatic children: a pilot study. *J R Soc Promot Health* 2004;124:74–80.

37. Murray CS, Poletti G, Kebadze T, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61:376–82.

38. Lee SL, Chiu SS, Malik PJ, et al. Is respiratory viral infection really an important trigger of asthma exacerbations in children? *Eur J Paediatr* 2011;170:1317–24.

39. Rabinovitch N, Strand M, Gelfand EW. Particulate levels are associated with early asthma worsening in children with persistent disease. *Am J Respir Crit Care Med* 2006;173:1098–105.

40. Rabinovitch N, Silveira L, Gelfand EW, et al. The response of children with asthma to ambient particulate is modified by tobacco smoke exposure. *Am J Respir Crit Care Med* 2011;184:1350–7.

41. Gillespie-Bennett J, Pierse N, Wickens K, et al. The respiratory health effects of nitrogen dioxide in children with asthma. *Eur Respir J* 2011;38:303–9.

42. Gotzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy* 2008;63:646–59.
Associations between environmental exposures and asthma control and exacerbations in young children – a systematic review

On line supplement
| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|--------------------------|------------------|--------|------------------|------------|-------------------|---------|
| Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children (2007) ¹ USA | Physician diagnosed asthma and symptoms in the previous year | Symptom score Peak expiratory flow | Longitudinal study | 1449 children presenting to emergency departments or attending clinics aged 4-9 years | Relate outcomes to exposures to ETS and indoor NO₂ | Urinary cotinine concentrations and indoor NO₂ concentrations (measured over a week in 663 houses) were measured at enrolment and 3, 6 and 9 months afterwards peak flow and symptoms were recorded (the latter over telephone) | Higher NO₂ (>53ppb) was linked to increased symptoms among non-atopic children (RR 1.8 [1.1, 2.8]. Exposure to ETS (cotinine/ creatinine >30ng/mg) and higher NO₂ were both associated with reduced peak flow (<80% predicted) during the winter months – RR 1.2 [1.0,1.5] and 15 [1.1, 2.0] respectively. |
| Environmental tobacco smoke and its effect on the symptoms and medication in children with asthma . (2009) ² Japan *POOR STUDY DESIGN* | Physician diagnosed asthma | Level of preventor medication needed | Cross sectional study | 282 asthmatic children 0-17 years of age (mean age 6.9 years) | To investigate the influence of second hand smoke on the symptoms of asthmatic children and its effect on the efficacy of their medication. | Information was gathered from parents and carers of the children on smoke exposure and medication. Data were also gathered for asthmatic symptoms and use of anti asthmatic drugs. | There was no significant difference for severity of asthmatic symptoms between the no/ mild ETS exposure groups compared with heavy ETS exposure group. Prevalence of anti asthmatic drug use of leukotriene receptor antagonists was significantly higher among the high ETS exposure group compared to the other group (p=0.002). |
| Study                                                                 | Definition of asthma used                                                                 | Outcome reported                                                                 | Design            | Study population                  | Objectives                                                                                                                                  | Programme content                                                                 | Outcome                                                                                           |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------------|
| Environmental tobacco smoke exposure and nocturnal symptoms among inner-city children with asthma (2002) 3USA | At least one of the following: (i) physician diagnosed asthma (ii) symptoms suggestive of asthma (iii) ED presentation with asthma | Symptom diary                                                                   | Cross sectional  | School children with asthma (n=590) | To examine the relationship among ETS exposure, select asthma symptoms and consequences among inner-city children with asthma. | Data were gathered from parents or carers on home ETS exposure, information on limited physical activity as a result of asthma related symptoms and number of school days missed. | Exposure to high levels of ETS was associated with a significant increase in the nocturnal symptoms in children (OR 2.83, 95% CI 1.22-6.55). |
| Association between exposure to environmental tobacco smoke and exacerbations of asthma in children (1993) 4USA *POOR STUDY DESIGN* | Children with asthma                                                                       | Exacerbation                                                                   | Cross sectional  | Asthmatic children (n=199)         | To study the association between exposure to ETS and asthma exacerbations in children.                                               | Data were collected in the form of urinary cotinine levels and pulmonary function tests were carried out. Data were gathered on exposure to ETS and episodes of acute exacerbations. | There was a significantly increased risk for acute exacerbations of asthma following exposure to ETS and this was dose dependent (RR 1.8, 95% CI 1.4-2.2-for reported exposure and RR 1.7, 95% CI 1.4-2.1- for exposure indicated cotinine levels). Forced expiratory volume in one second (FEV₁) decreased with increases in both measures of exposure. |

### Air quality

#### Ozone

| Acute respiratory | Persistent | Asthma | Longitudinal | 861 children from | To relate outdoor air | After recruitment, | Air pollutant |
|-------------------|------------|--------|--------------|--------------------|-----------------------|--------------------|---------------|

- [1](#) Source reference: [1.](#) - [2.](#) Source reference: [2.](#) - [3.](#) Source reference: [3.](#) - [4.](#) Source reference: [4.](#)
| Study                                                                 | Definition of asthma used                                                                 | Outcome reported                  | Design     | Study population                                      | Objectives                                                                                                                                  | Programme content                                                                 | Outcome                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------|------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| health effects of air pollution on children with asthma in US inner cities (2008) | asthma and positive skin prick test                                                      | symptoms, school days missed, peak flow and FEV₁ | al study   | inner cities aged 5-12 years (mean age 7.7 years)    | quality (NO₂, SO₂, PM₂.₅, CO and O₃) to symptoms and lung function over 2 years                                                                 | symptoms were captured by 2-monthly telephone calls. Children completed spirometry each 6 months. Increases in routinely acquired air quality data (from the 10th to 90th centile) were related to symptoms and spirometry. | concentrations were within recommended limits. In single pollutant models, NO₂, SO₂ and PM₂.₅ (but not CO or O₃) were related to outcomes. In a 3-pollutant model, increased NO₂ was associated with increased cough and wheeze (OR 1.2 [95% CI 1.0, 1.5] and reduced %FEV₁ (mean reduction 1.1% [95% CI 0.4, 1.8]). Increased PM₂.₅ exposures were linked to reduced FEV₁ (mean reduction 0.7% [95% CI 0.1, 1.3]) |
| breast effect of air pollution on inner-city children with asthma (2002) | Physician-diagnosed asthma and/or asthma symptoms in the previous year                    | Peak Expiratory Flow             | Longitudinal | Children (n=846) 4-9 years of age                | To examine the effect of daily ambient air pollution among children residing in urban areas.                                                                 | Data collected over 4 months for respiratory symptoms, air pollutant concentrations and lung function | Exposure to Ozone was associated with a 59% decline in PEFR (95% CI 0.13-1.05). Even at levels below then current USA air quality standards, summer air pollution was linked to decreased pulmonary function among the children. |
| Chronic exposure to ambient ozone                                    | Hospital                                                                                 | Asthma admission                 | Longitudinal | Children (n=1204396) 1-6                          | To investigate impact of high ozone levels on                                                                                               | Data collected on ozone concentrations and                                      | Chronic exposure to Ozone may increase risk                               |
| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|--------------------------|------------------|--------|------------------|------------|-------------------|---------|
| and asthma hospital admissions among children (2008)<sup>7</sup> USA | record of admission with asthma (infants excluded) | | years of age | childhood asthma admissions. | asthma admissions. | of asthma admissions (OR 1.16, 95% CI 1.15-1.17). |
| In-home particulate concentrations and childhood asthma morbidity (2009)<sup>8</sup> USA | Physician diagnosed asthma plus medication/ symptoms in previous 6 months | Symptoms and reliever medication use | Longitudinal | 150 children aged 2-6 years. 91% African Americans | Relate bedroom PM<sub>2.5</sub> and PM<sub>2.5-10</sub> exposures at baseline and 3 and 6 months afterwards to daily diary scores | Particulate exposures were measured at 3 month intervals over 6 months. Parents completed daily diaries. | Each increase of 10μg/m<sup>3</sup> PM<sub>2.5-10</sub> exposure was associated with a 6% increase in asthma symptoms [95% CI 1-12] and 6% increase in reliever medication [95% CI 1-10]. 3% and 4% increase in symptoms and reliever use were associated with a 10μg/m<sup>3</sup> increase in PM<sub>2.5</sub> exposure. |
| Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma (2011)<sup>9</sup> USA | Same cohort as above<sup>8</sup> | Same cohort as above<sup>8</sup> | Same cohort as above<sup>8</sup> | Same cohort as above<sup>8</sup> | Same cohort as above<sup>8</sup> | Same cohort as above<sup>8</sup> | PM<sub>2.5-10</sub> exposures were comparable for atopic and non-atopic children. PM<sub>2.5</sub> exposures were higher for non-atopic compared to atopic children (36 vs 28 μg/m<sup>3</sup>). Increasing PM exposure was associated with increased risk for symptoms in atopic and non-atopic children. |
| Study and country | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|------------------|---------------------------|------------------|--------|------------------|------------|------------------|---------|
| Household levels of nitrogen dioxide and pediatric asthma severity (2013) USA | At least two out of the following: Physician diagnosed asthma, asthma symptoms in previous 12 months, asthma treatment within the previous 12 months | Symptoms and reliever medication use | Longitudinal study | 1342 children aged 5-10 years (52% aged <8 years) | To relate indoor NO\textsubscript{2} exposure to asthma outcomes in children | NO\textsubscript{2} was measured over one month using Palms tubes at baseline and at 3 months intervals over the next 12 months. Asthma outcomes were determined by telephone interviews which were held at the end of each NO\textsubscript{2} measurement period. Exposure to indoor allergens including HDM, cat, dog and cockroach was also measured | NO\textsubscript{2} exposure was expressed as quintiles and the reference was the lowest two quintiles combined. Children in the fourth and fifth quintiles of (highest) exposure were at increased risk for all outcomes. The fifth quintile were more likely to wheeze (OR 1.5 [95% CI 1.2, 2.0]) and to have rescue medication use (OR 1.7 [95% CI 1.3, 2.3]). |
| Association of indoor nitrogen dioxide exposure | Physician diagnosed asthma | Symptoms | Cross sectional | 728 children aged <12 years (67%<6 years) | Relate indoor NO\textsubscript{2} concentrations to symptoms over the previous month | Respiratory symptoms over the previous month were determined by | NO\textsubscript{2} concentrations were higher in homes with gas stoves. Each 20ppb |
| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| with respiratory symptoms in children with asthma (2006) 11 USA | | | whose newborn sibling had been recruited onto a trial (inclusion criteria were older sibling with asthma) | previous month | research administered questionnaire. NO₂ was measured over the following 10-14 days using (Palme tubes). | increase in NO₂ was associated with increased wheeze (OR 1.5 [1.0, 2.2]) and chest tightness (OR 1.6 [1.0, 2.5]) |

**Damp housing, mould**

| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources.. (2006) 12 USA | Presentation to emergency department of primary care or hospitalisation with acute asthma | Symptoms | RCT, follow-up period one year | Children with asthma (n=62) 2-17 years of age. Intervention n=29, Controls n=33 | To examine the changes in asthma morbidity in children following home remediation aimed at moisture sources. | Both groups received an asthma intervention (action plan, education and individualized problem solving). Intervention group also received household repair, removal of water damaged building materials and heating, ventilation and air conditioning alterations. | There was a significant decrease in symptom days in the intervention group (p=0.003) |

| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children (2010) 13 USA | Moderate-to-severe asthma with positive skin test to at least one fungal allergen | Symptom score (daytime, night time and exertional symptoms) and unscheduled ED or | Longitudinal study | 469 children aged 5-11 years (mean 7.7 years) out of 936 children screened (467 with no positive skin test) | To relate indoor and outdoor fungal exposures to asthma symptoms over 2 years. | Fungal exposures were measured at baseline and 6 monthly thereafter. Symptoms were obtained from 2 monthly telephone consultations | Indoor and outdoor fungal exposures were positively associated with outcome. When both were considered, only indoor exposures were associated with outcomes. A 10-fold increase in total fungal exposure was positively related to risk for |
### Inhaled allergens (house dust mite, pets, pollens)

| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| House Dust Mite-Free Pillow on Clinical Course of Asthma and IgE Level—A Randomized, Double-Blind, Controlled Study. (2008) 14Japan | Medical follow up for asthma in hospital clinic. HDM sensitised. | Symptoms | Intervention 12 months | Intervention (n=10) mean age 7, range 5-11 years and controls (n=10) mean age 6; range (4-8). | To investigate HDM and fungi contamination of HDM-free pillows and the effects of these pillows on clinical courses of asthmatic children with house dust allergy. | Intervention group were provided with HDM free pillows and control group used new common pillows with HDM permeable fabrics. Samples were collected for fungi and HDM allergen Der 1 detection at three intervals. | Asthma symptoms did not differ between intervention and control groups. There were no significant differences in the levels of HDM allergen Der 1 between the groups. Among children with high HD-IgE levels (≥ 50 U/mL) before the study, the levels had decreased after 12 months in all six subjects in the intervention group (p=0.030; paired t-test) and in four of seven subjects in the placebo group (p=0.481; paired t-test). |
| Effect of mattress | Level of | Interventio | Children (n=60) | To investigate whether | Active treatment group | Significant reduction in | |

Increased Penicillium exposure was positively associated with exacerbation (OR 1.2, [1.0, 1.3] and also with symptoms (mean increased number of symptomatic days 1.2)
| Study                                                                 | Definition of asthma used                                                                 | Outcome reported                                                                 | Design                                           | Study population                  | Objectives                                                                                                           | Programme content                                                                                         | Outcome                                                                                                  |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| and pillow encasings on children with asthma and house dust mite allergy (2003)                                   | Physician diagnosed asthma, HDM skin prick positive and BHR to inhaled HDM              | n with one year follow-up period                                                  | 6-15 years old with asthma and allergy to house dust mite. | Mattress and pillow encasings resulted in an effective long-term control of HDM allergen levels, thereby reducing the need for asthma medication in children with asthma and HDM allergy. | was provided mattress and pillow encasings coated with semi permeable polyurethane. Control group received a placebo mattress and pillow covers. | HDM allergen was observed in the active treatment group (p=0.032). After 12 months there was a reduction in the dose of inhaled steroids by 50% in significantly more children in the active treatment group vs. the control group (73% vs. 24%, p<0.001). |
| Does a multifaceted environmental intervention alter the impact of asthma on inner-city children?. (2006)       | Asthma admission or presentation to emergency department                                | Symptoms                                                                         | RCT                                             | Children (5-12 years of age, trial period one year) | To evaluate the impact of an environmental and educational intervention on the indoor environment and health in children with asthma living in urban environments. | Children were randomized into intervention (n=84) and delayed intervention (n=77) groups. Interventions were delivered by trained community health workers and focused on reduction of HDM and cockroach allergen, reduction in exposure to ETS, professional cleaning and health education. Asthma severity scores were determined, house dust assays were carried out and blood samples were collected from children. | There was no change in the asthma severity scores between the groups.                                      |
| Study                                                                 | Definition of asthma used                                                                 | Outcome reported                                                                 | Design            | Study population                        | Objectives                                                                                                                                                                                                                                                                                                                                 | Programme content                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Outcome                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Results of a home-based environmental intervention among urban children with asthma. (2004) USA *STRONG STUDY DESIGN* | Asthma diagnosed by study physician, exacerbation in past 6 months and skin prick positive. | Symptoms                                                                         | Interventions RCT one year | Children (n=937) aged 5-11 years of age with mild to moderate asthma. Intervention n=469, control n=468. | To determine whether an environmental intervention tailored to each child’s allergic sensitization and environmental risk factors could improve asthma-related outcomes. | Baseline data were collected for complications related to asthma and information on home environment (dust samples). Carers of children in the intervention group received education, skills, motivation, equipment and supplies to perform environmental remediation. Control group received visits only every six months. | Intervention group had significantly fewer days with symptoms compared to the control group both 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). |
| Environmental intervention for house dust mite control in childhood bronchial asthma (2012) Egypt | Physician diagnosed asthma and asthma treatment within the last 6 months and skin prick positive to HDM | Asthma severity and spirometry (FEV₁)                                             | RCT               | 160 children aged 5-12 (mean 7.7 years) | To determine whether chemical HDM measures (twice weekly sparing with tannic acid) or physical measures (multiple including ventilation, HDM impermeable bedding) or both are superior to standard care | A 16 week trial. After randomisation, home visits each 2 weeks to ensure compliance. Outcomes measures at 8 and 16 weeks. | No significant difference in severity- evidence for reduced prevalence of most severe symptoms. Improvement of approximately 2% in FEV₁ for children in each of the 3 active arms of the trial. |
| Study                                                                 | Definition of asthma used                                                                 | Outcome reported                  | Design                          | Study population                  | Objectives                                                                 | Programme content                                                                 | Outcome                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------|-----------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Healthy Homes University: a home-based environmental intervention and education program for families with pediatric asthma in Michigan (2011) | Care giver reported asthma                                                                 | Symptoms Seeking unscheduled health care | Single arm intervention study    | 243 households, index case aged under 12 in 80% | To determine whether complex intervention improved asthma outcomes | Complex intervention including removing asthma triggers, asthma education and also addressing injury hazards. Interventions included removing moisture from the house, removing carpets, air filter unit, HDM impermeable bedding, smoking education. 4 visits to encourage compliance over 6 months | Improved reported symptoms after 6 months (between 1-7% for different symptoms). 47% reduction in unscheduled healthcare visits. |
| Effects of ambient pollen concentrations on frequency and severity of asthma symptoms among asthmatic children (2012) | Physician diagnosed asthma and symptoms in previous 6 months | Symptom score and reliever medication use | Longitudinal study | 430 children aged 4-12 (44% <8 years) sensitised and not sensitised to pollens (predominantly ragweed) | To relate asthma symptoms and rescue medication use to changes in pollen exposure during one pollen season (April-September) | At recruitment sensitisation status and use of maintenance treatment were established. Pollen exposure was estimated using a previously validated model. Ambient PM$_{2.5}$, O$_3$, NO$_2$ and SO$_2$ were included in the analysis | Among children on maintenance treatment and sensitised to grass and weed, risk for symptoms and rescue medication use were increased in all quintile of exposure compared to the lowest quintile. The greatest risk was seen among those exposure to the second highest quintile of pollen exposure: OR for wheeze 2.4 [95%CI 1.5, 3.7] and OR for rescue medication |
| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. (2001) | ≥3 episodes of wheeze | Longitudinal study | Children (n=183) age 1-4 years diagnosed with asthma. | To evaluate the importance of early exposure to pets and other environmental risk factors in asthmatic children. | Questionnaire data were collected for family history of atopic disease and indoor environmental conditions. Serum IgE antibodies to cat and dog were measured. Asthma severity scored at structured interview with a parent. Floor dust collected from home and analyzed for FelD1 and Can f 1. | Children with exposure to cats during the first 2 years of life were more likely to have developed sensitisation by 4 years of age compared to unexposed children (OR 5.6 [95% CI 1.06, 29.0]. High levels of cat allergen (Fel D1≥8 μg/g dust) were associated with an increased risk of sensitisation to cat and in combination with ETS with more severe asthma. |

**Industrial incineration, coal**-No evidence

**Fireworks**- No evidence

**Domestic combustion (solid fuel, gas and candles)**

| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. (2008) | Physician diagnosed asthma and symptoms in the past 12 months. | Symptoms Spirometry | RCT | Children (n=349) Intervention n=175, control n=174. | To assess whether non-polluting, more effective home heating has a positive effect on the health of children with asthma. | Intervention group received a non polluting more effective home heater before winter. Control group received a replacement heater at the end of the trial. | No significant improvements observed in lung function. There was a significant reduction in asthma symptoms (OR=0.48, 95% CI 0.31-0.74, p<0.001) |
| Study                                                                 | Definition of asthma used                                      | Outcome reported           | Design      | Study population                                                                 | Objectives                                                                                     | Programme content                                                                 | Outcome                                                                                     |
|---------------------------------------------------------------------|----------------------------------------------------------------|---------------------------|-------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Randomized controlled trial of unfluenced gas heater replacement on respiratory health of asthmatic schoolchildren (2004) 23 Australia *POOR STUDY DESIGN* | Physician diagnosed asthma                                    | Symptoms                  | RCT         | Intervention (n=45) mean age 8.4, SD 2.2; Control (n=68) mean age 8.7, SD 2.3.  | To investigate the effect of replacing unfluenced gas heaters on respiratory health of asthmatic children. | In intervention schools unfluenced gas heaters were replaced with flued gas or electric heaters. No heaters were replaced in the control school. Information on symptoms was collected using daily diaries, lung function tests were carried out and data on NO2 was collected using passive diffusion badge monitors. | There was a significant reduction in asthma symptoms in the children from intervention schools. 1) Difficulty breathing during day RR=0.41, 95% CI 0.07-0.98. 2) Difficulty breathing during night RR=0.32, 95% CI 0.14-0.69. 3) Daytime asthma attacks RR=0.39, 95% CI 0.17-0.93. |

**Vacuum - No evidence**

**Air conditioning and Humidifiers**

| Study                                                                 | Definition of asthma used                                      | Outcome reported           | Design      | Study population                                                                 | Objectives                                                                                     | Programme content                                                                 | Outcome                                                                                     |
|---------------------------------------------------------------------|----------------------------------------------------------------|---------------------------|-------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Humidity control for chronic asthma. Cochrane Database Systematic Rev. (2008) 24 UK | Attending hospital asthma clinic                                | Systematic Review          | One RCT 25 (13 adults and 27 children age 4-16 years)                             | To study the effect of dehumidification of the home environment on asthma control.             | Study participants were grouped into those who received 1) fixed humidifiers, 2) MVHR, 3) High efficiency vacuum cleaners and 4) No intervention | Although there was a significant decline in the house dust mite count and antigen levels in group 1 and group 2, no clinical benefit was observed in the asthmatic patients. |
| Study | Definition of asthma used | Outcome reported | Design | Study population | Objectives | Programme content | Outcome |
|-------|---------------------------|------------------|--------|------------------|------------|-------------------|---------|
| **Allergens in diet** | The effects of exclusion of dietary egg and milk in the management of asthmatic children: a pilot study (2004) **26UK** | Physician diagnosed mild or moderate asthma | Peak expiratory flow | RCT (8 weeks) | Asthmatic children (n=22) aged 3-14 years, Intervention n=13, control n=9. | To determine the potential benefits of dietary avoidance of egg and egg products and milk and milk products in reducing the symptoms of asthma in children. | Intervention group participants were asked to adhere to a diet devoid of egg and egg products and milk and milk products. Those in the control group were asked to continue to eat their usual diet. | Amongst the intervention group the mean value for peak expiratory flow rate (PEFR) measurement had risen by 22% (p<0.05) whereas there was a decrease in mean PEFR value by 0.6% in the control group. |
| **Viruses** | Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. (2006) **27UK** | Admitted to hospital with asthma or attending hospital asthma clinic | Asthma admission | Case control study | Children aged 3-17 years of age (n=84) | To investigate the importance of allergen exposure in sensitised individuals in combination with viral infections and other potentially modifiable risk factors precipitating asthma admissions in children. | Cases were children admitted over a one year period (acute asthmatics) matched with two groups of controls: those with stable asthma and children admitted with non respiratory conditions. | A combination of virus detection and allergen sensitization significantly increased risk of hospital admission among the acute asthmatics in comparison to the controls (OR 19.4, 95% CI 3.7-101.5, p<0.001) |
| Is respiratory viral infection really an important trigger of asthma | Physician diagnosed asthma, symptoms in previous year, Presence of virus in mild exacerbation | Longitudinal study | 114 children aged 6-1 4 years (mean age not stated) | To determine whether respiratory viruses were associated with asthma exacerbations | After recruitment, children completed diaries and twice daily peak flow. If peak flow was ≤80% baseline, | Over 12-15 months, there were 305 respiratory illnesses in 98 children presented for clinical assessment. 166 samples |
| Study                                      | Definition of asthma used                                                                 | Outcome reported | Design | Study population | Objectives                                                                 | Programme content                                                                                           | Outcome                                                                                           |
|-------------------------------------------|------------------------------------------------------------------------------------------|------------------|--------|------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| exacerbations in children? (2011) 28 Hong Kong | no hospitalisation s and on ≤400 microg inhaled steroids daily (BUD equivalent)           |                  |        |                  | symptom score exceeded the predetermined threshold or parents felt their child had a cold then the child attended an clinical assessment which included collecting samples for viral testing (immune fluorescence and some PCR) | were collected (54% of episodes) from which respiratory virus was identified in only 61. Approximately half of episodes were considered asthma exacerbations, the remainder respiratory infections. |
Table II. Summary of the quality control exercise. Each of the six individual domains and the global rating is scored as follows: 1=strong, 2=moderate and 3=weak. The paper\textsuperscript{25} which was included in the systematic review\textsuperscript{24} for the use of humidification was used for the quality control.

| Study          | Selection Bias | Study Design | Confounders | Blinding | Data Collection Methods | Withdrawals and Drop-outs | Global Rating |
|----------------|----------------|--------------|-------------|----------|-------------------------|----------------------------|---------------|
| Kattan \textsuperscript{1} | 2              | 2            | n/a         | 2        | 1                       | 1                          | 2             |
| Yamasaki et al. \textsuperscript{2} | 3              | 3            | n/a         | 3        | 3                       | 2                          | 3             |
| Morkajaroenpong \textsuperscript{3} | 2              | 3            | n/a         | 2        | 1                       | 1                          | 2             |
| Chimonczyk \textsuperscript{4} | 3              | 3            | n/a         | 2        | 3                       | 1                          | 3             |
| O'Connor \textsuperscript{5} | 2              | 2            | n/a         | 2        | 1                       | 1                          | 2             |
| Mortimer \textsuperscript{6} | 3              | 2            | n/a         | 2        | 1                       | 2                          | 2             |
| Lin \textsuperscript{7} | 2              | 2            | n/a         | 2        | 1                       | 2                          | 2             |
| McCormick \textsuperscript{8} | 2              | 2            | n/a         | 2        | 1                       | 3                          | 2             |
| McCormick \textsuperscript{9} | 2              | 2            | n/a         | 2        | 1                       | 1                          | 2             |
| Belanger 2013\textsuperscript{10} | 3              | 2            | n/a         | 2        | 1                       | 1                          | 2             |
| Belanger 2006\textsuperscript{11} | 2              | 3            | n/a         | 2        | 1                       | 1                          | 2             |
| Kercsmar 2006\textsuperscript{12} | 3              | 1            | 1           | 1        | 1                       | 1                          | 2             |
| Name           | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---------------|---|---|---|---|---|---|---|---|
| Pongracic     | 3 | 2 | 1 | 2 | 1 | 1 | 1 | 2 |
| Nambu         | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| Halken        | 3 | 1 | 1 | 1 | 2 | 2 | 2 | 2 |
| Williams      | 3 | 1 | 1 | 3 | 3 | 3 | 3 | 3 |
| Morgan        | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 |
| El Ghitany    | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
| Largo         | 3 | 2 | n/a| 3 | 1 | 2 | 3 | 3 |
| Delavalle     | 2 | 2 | n/a| 2 | 1 | 1 | 1 | 2 |
| Melen         | 2 | 2 | n/a| 2 | 1 | 1 | 2 | 2 |
| Howden-       | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Chapman       |    |   |   |   |   |   |   |   |
| Pilotto       | 3 | 1 | 1 | 1 | 1 | 1 | 3 | 3 |
| Warner        | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 2 |
| Yusoff        | 3 | 2 | 1 | 2 | 1 | 1 | 1 | 2 |
| Murray        | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 2 |
| Lee           | 2 | 2 | n/a| 2 | 1 | 1 | 1 | 2 |
REFERENCES

1. Kattan M, Gergen PJ, Eggleston P, Visness CM, Mitchell HE. Health effects of indoor nitrogen dioxide and passive smoking on urban asthmatic children. *J Allergy Clin Immunol* 2007;120:618-24.
2. Yamasaki A, Hanaki K, Tomita K, et al. Environmental tobacco smoke and its effect on the symptoms and medication in children with asthma. *Int J Environ Health Res* 2009;19:97-108.
3. Morkjaroenpong V, Rand CS, Butz AM, et al. Environmental tobacco smoke exposure and nocturnal symptoms among inner-city children with asthma. *J Allergy Clin Immunol* 2002;110:147-53.
4. Chilmonczyk BA, Salmun LM, Megathlin KN, et al. Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *N Engl J Med* 1993;328:1665-9.
5. O'Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;121:1133-1139.
6. Mortimer KM, Neas LM, Dockery DW, Redline S, Tager IB. The effect of air pollution on inner-city children with asthma. *Eur Respir J* 2002;19:699-705.
7. Lin S, Liu X, Le LH, Hwang SA. Chronic exposure to ambient ozone and asthma hospital admissions among children. *Environ Health Perspect* 2008;116:1725-30.
8. McCormack MC, Breyssse PN, Matsui EC, et al. In-home particle concentrations and childhood asthma morbidity. *Env Health Perspect* 2009;117:294-8.
9. McCormack MC, Breyssse PN, Matsui EC, et al. Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma Immunol* 2011;106:308-15.
10. Belanger K, Holford TR, Gent JF, Hill ME, Kezik JM, Leaderer BP. Household levels of nitrogen dioxide and pediatric asthma severity. *Epidemiol* 2013;24:320-30.
11. Belanger K, Gent JF, Triche EW, Bracken MB, Leaderer BP. Association of indoor nitrogen dioxide exposure with respiratory symptoms in children with asthma. *Am J Respir Crit Care Med* 2006;173:297-303.
12. Kercsmar CM, Dearborn DG, Schluchter M, et al. Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. *Environ Health Persp* 2006;114:1574-80.
13. Pongracic JA, O'Connor GT, Muilenberg ML, et al. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. *J Allergy Clin Immunol* 2010;125:593-9.
14. Nambu M, Shirai H, Sakaguchi M, Aihara M, Kakatori T. Effect of House Dust Mite-Free Pillow on Clinical Course of Asthma and IgE Level—A Randomized, Double-Blind, Controlled Study. *Paediatr Allergy Immunol* 2008;21:137-144.
15. Halken S, Host A, Niklasson U, et al. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol* 2003;111:169-76.
16. Williams SG, Brown CM, Falter KH, et al. Does a multifaceted environmental intervention alter the impact of asthma on inner-city children? *J Nat Med Assoc* 2006;98:249-60.

17. Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351:1068-80.

18. El-Ghitany EM, Abd El-Salam MM. Environmental intervention for house dust mite control in childhood bronchial asthma. *Environ Health Prev Med* 2012;17:377-84.

19. Largo TW, Borgialli M, Wisinski CL, Wahl RL, Priem WF. Healthy Homes University: a home-based environmental intervention and education program for families with pediatric asthma in Michigan. *Public Health Reports* 2011;126 (suppl 1):14-26.

20. DellaValle CT, Triche EW, Leaderer BP, Bell ML. Effects of ambient pollen concentrations on frequency and severity of asthma symptoms among asthmatic children. *Epidemiol* 2012;23:55-63.

21. Melen E, Wickman M, Nordvall SL, van Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. *Allergy* 2001;56:646-52.

22. Howden-Chapman P, Pierse N, Nicholls S, et al. Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. *Brit Med J* 2008;337:a1411.

23. Pilotto LS, Nitschke M, Smith BJ, et al. Randomized controlled trial of unflued gas heater replacement on respiratory health of asthmatic schoolchildren. *Int J Epidemiol* 2004;33:208-14.

24. Singh M, Bara A, Gibson P. Humidity control for chronic asthma. *Cochrane Database Systematic Rev* 2002;2.

25. Warner JA, Frederick JM, Bryant TN, et al. Mechanical ventilation and high-efficiency vacuum cleaning: A combined strategy of mite and mite allergen reduction in the control of mite-sensitive asthma. *J Allergy Clin Immunol* 2000;105:75-82.

26. Yusoff NA, Hampton SM, Dickerson JW, Morgan JB. The effects of exclusion of dietary egg and milk in the management of asthmatic children: a pilot study. *J Roy Soc Promotion Health* 2004;124:74-80.

27. Murray CS, Poletti G, Kebadze T, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61:376-82.

28. Lee SL, Chiu SS, Malik PJ, Chan KH, Wong HS, Lau YL. Is respiratory viral infection really an important trigger of asthma exacerbations in children? *Eur J Paed* 2011;170:1317-24.
Search strategy

1. Asthma/
2. wheeze.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. atopy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. hayfever.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. Allergens/
6. Bronchial Spasm/
7. reactive airway disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. Bronchial Hyperreactivity/
9. environmental factors.mp.
10. environmental influences.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. environmental exposure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
13. 9 and 12
14. 10 and 12
15. 11 and 12
16. 13 or 14 or 15
17. environmental tobacco smoke.mp.
18. 1 or 2 or 3 or 4 or 6 or 7 or 8
19. 17 and 18
20. in utero exposure.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. 17 and 20
22. maternal smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. 18 and 22
24. parental smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. 18 and 24
26. Cotinine/
27. 18 and 26
28. 18 and 21
29. 19 or 23 or 25 or 27 or 28
30. limit 29 to (english language and humans and ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)"
and english and humans)
31. from 30 keep 1-599
32. Nitrogen Dioxide/
33. gas fire*.mp.
34. cooker*.mp.
35. hob*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
36. 32 or 33 or 34 or 35
37. 18 and 36
38. Volatile Organic Compounds/
39. cleaning agents.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
40. chemicals.mp.
41. glue*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
42. floor covering*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
43. dry cleaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
44. Chlorine/
45. swimming pool*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
46. Solvents/
47. Benzene/
48. resin*.mp.
49. varnish.mp.
50. Paint/
51. ethyl benzene.mp.
52. air fresheners.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
53. toluene.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
54. caulk*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
55. Formaldehyde/
56. 18 and 38
57. 18 and 39
58. 18 and 40
59. 18 and 41
60. 18 and 42
61. 18 and 43
62. 18 and 44
63. 18 and 45
64. 18 and 46
65. 18 and 47
66. 18 and 48
67. 18 and 49
68. 18 and 50
69. 18 and 51
70. 18 and 52
71. 18 and 53
72. 18 and 54
73. 18 and 55
74. 56 or 57 or 58 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75. Vehicle Emissions/ae, pc, to [Adverse Effects, Prevention & Control, Toxicity]
76. plastic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
77. phthalate$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
78. flame retardant$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
79. plasticizer$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
80. plasticiz$ polyvinyl chloride.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
81. floor covering$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
82. adhesive$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
83. synthetic leather.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
84. toy$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
85. cosmetic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
86. indoor dust.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
87. di 2-ethylhexyl phthalate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
88. 18 and 75
89. 18 and 76
90. 18 and 77
91. 18 and 78
92. 18 and 79
93. pvc.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
94. 18 and 93
95. 18 and 81
96. 18 and 82
97. 18 and 83
102. outdoor source$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
103. ozone.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
104. sulphur dioxide.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
105. traffic.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
106. exhaust.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
107. coal fire$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
108. diesel.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
109. weather.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
110. 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111. 18 and 110
112. particulate matter.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
113. UFP$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
114. transport.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
115. industrial incineration.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
116. firework$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
117. bonfire.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
118. solid fuel.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
119. heating$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
120. cooking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
121. candle$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
122. vacuum$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
123. hoover$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
124. resuspension.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
125. ingressio.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
126. incineration.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
127. 112 or 113 or 114 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126
128. 18 and 127
129. NOX.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
130. 32 or 33 or 34 or 35 or 129
131. 18 and 130
132. curtain*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
133. carpet*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
134. 18 and 132
135. 18 and 133
136. 88 or 89 or 90 or 91 or 92 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 134 or 135
137. tetraethyl lead.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
138. 18 and 137
139. cerium oxide*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
140. 18 and 139
141. cold air.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
142. 18 and 141
143. meteorolog*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
144. 18 and 143
145. temperature.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
146. 18 and 145
147. climate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
148. 18 and 147
149. 111 or 142 or 144 or 146 or 148
150. air pollut*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
151. 18 and 150
152. total suspended particulate*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
153. 18 and 152
154. coal.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
155. 18 and 154
156. wood.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
157. 18 and 156
158. peat.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
159. 18 and 158
160. biomass.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
161. 18 and 160
162. oil.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
163. 18 and 162
164. diacetyl.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
165. 18 and 164
166. 128 or 151 or 153 or 155 or 157 or 159 or 161 or 163 or 165
167. allergens.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
168. aspergillus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
169. cladosporium.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
170. dust mite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
171. cat*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
172. dog*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
173. horse*.mp.
174. animal*.mp.
175. pet*.mp.
176. mould.mp.
177. mold.mp.
178. alternaria.mp.
179. cockroach*.mp.
180. mice.mp.
181. rats.mp.
182. pollen.mp.
183. grass.mp.
184. aeroallergen*.mp.
185. IgE.mp.
186. fungal spore*.mp.
187. food allerg*.mp.
188. glucan*.mp.
189. peanut*.mp.
190. egg.mp.
191. milk.mp.
192. dairy.mp.
193. 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192
194. 18 and 193
195. exercise.mp.
196. 18 and 195
197. lipopolysaccharide.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
198. 18 and 197
199. endotoxin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
200. 18 and 199
201. respiratory syncitial virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
202. 18 and 201
203. rhinovirus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
204. 18 and 203
205. influenza virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
206. 18 and 205
207. corona virus.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
208. 18 and 207
209. 202 or 204 or 206
210. diet.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
211. 18 and 210
212. sulphite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
213. sulfite*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
214. sodium metabisul*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
215. monosodium glutamate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
216. MSG.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
217. sodium benzoate.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
218. vitamin D.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
219. vitamin E.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
220. antioxidant*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
221. lipid*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
222. 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221
223. 18 and 222
224. 211 or 223
225. breastfeeding.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
226. weaning.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
227. 225 or 226
228. 18 and 227
229. drug*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
230. 18 and 229
231. aspirin.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
232. paracetamol.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
233. antibiotic*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
234. NSAID*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
235. 231 or 232 or 233 or 234
236. 18 and 235
237. obesity.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
238. 18 and 237
239. 29 or 131 or 136 or 149 or 166 or 194 or 198 or 200 or 209 or 224 or 228 or 236 or 238
240. 9 or 10 or 11
241. 18 and 240
242. 239 or 241
243. 74 or 242
244. limit 243 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)") and english and humans and (case reports or classical article or comparative study or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or "corrected and republished article" or government publications or guideline or historical article or introductory
journal article or journal article or meta analysis or multicenter study or patient education handout or periodical index or randomized controlled trial or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or "review" or "scientific integrity review" or twin study or validation studies))
245. from 244 keep 6033,6045,6055,6062,6065,6091,6122,6150,6166,6172,6179,6225,6229-6230,6245,6249,6304,6307-6309,6315,6317,6346,6413-6414,6428,6435,6441,6453,6516,6551-6552,6574,6581,6585,6588,6599,6622,6641,6660,6699
246. from 244 keep 6710,6783