



EDPHiS



Contract Number: IOM/848/08

EDPHiS

Environmental Determinants of Public Health in Scotland

D.3 – Literature Review: Asthma Case Study

Project Start Date: 1 April 2008

Duration: 4 years



EDPHiS



**Environmental Determinants of Public Health in
Scotland (EDPHiS)**

Asthma case study

Scoping report

Jon Ayres

Steve Turner

Emma Doust

Yvette Christopher

Amy Shafrir

Hilary Cowie

August 2009

FOREWORD

EDPHiS and its role in relation to Good Places, Better Health

EDPHiS (Environmental Determinants of Public Health in Scotland) is a multi-disciplinary collaborative scientific project, funded by the Scottish Government, and designed to inform the development of policy on environment and health in Scotland. As such, EDPHiS is one of the four components of the Intelligence Partnership of Good Places, Better Health (GPBH), whose current (Prototype) phase focuses on how young people in Scotland experience the physical environment, and how that impacts on the four GPBH priority health-related effects of obesity, unintentional injuries, asthma, and mental health and well-being.

GPBH is concerned ultimately with protecting and improving the health of Scotland's young people, and reducing health inequalities among them, by identifying and informing the implementation of policies and actions which protect and improve health through improvements to the physical environment in Scotland, and how young people interact with it. Within the GPBH Intelligence Partnership (IP), and working closely with the other IP partners, EDPHiS helps to inform this development of policy by:

- a. Providing evidence reviews of the international scientific literature concerning how the environment affects the lives and health of young people, up to ages 8 or 9 years; and in particular (i) how environmental exposures of young people affect their risks and chances in relation to the four priority health-related effects of GPBH; and (ii) what evidence there is from studies internationally of the success (or not) of interventions intended to improve children's health via the environment.
- b. Working with others in the IP and in Scotland more widely to identify relevant sources of information about Scotland in terms of population, environment, health and other contextual factors that may affect the relationships between environment and health.
- c. Linking these to provide – as far as the scientific evidence and data allow – estimates of the likely benefits to children in Scotland of policies and actions that may affect their health via changes to the environment and/or how children interact with that environment. These estimates also will include an assessment of how the public health effects are distributed across age, gender, urban-rural and indices of social deprivation.

Evidence reviews of the international literature

These were designed to consider in turn the four priority health impacts of the GPBH Prototype, and to be carried out in two phases: First, a preliminary assessment of the evidence to scope approximately the issues to be addressed and to see what kind of evidence there was about them (Phase 1);

then, a more detailed and focused assessment aiming to provide quantitative evidence of those relationships which were identified as most relevant and important (Phase 2).

The present set of preliminary evidence assessments

The present set of preliminary evidence assessments took as a starting-point a diagrammatic representation (a 'map') of the relationships linking environment, exposure and health effect, developed using the modified DPSEEA modelling framework (Morris et al., 2006: Getting Strategic about the Environment and Health) adopted by GPBH. These maps were developed in a series of workshops, led by George Morris and Sheila Beck, where experts summarised current best thinking about how the environment relates to and affects public health.

Where maps were as yet unavailable for the priority health effects in young people, or were limited in scope, they were developed further or from new by the EDPHiS team as part of the preliminary evidence assessment. The main focus of the work thereafter was to consider the relationships proposed by the DPSEEA maps and to make a first assessment of the strength of evidence underlying them, especially insofar as that evidence is relevant to Scotland and its young people.

Following the DPSEEA framework, the Phase 1 reports focus both on (i) the Drivers and Pressures which influence the State of the environment, and the behaviours of children in interacting with it, and (ii) relationships between State of the environment, Exposures (i.e. interactions, whether favourable or unfavourable to health, of young people with the environment), and health Effects; with attention throughout on Actions which might improve children's environment and health.

The present set of four reports is the outcome of these preliminary assessments, which largely were completed about 12 months ago. Each of the four reports is the work of a particular multi-disciplinary team within EDPHiS, and so the reports are individually authored accordingly.

Taking the reports as a set, they represent a compromise between a desire for consistency of approach, and the need to allow differences according to (i) health effect, what it means and how it is measured; (ii) the complexity of the issues that arise in the relationships of environment to that health effect in children; and (iii) the strength and maturity of evidence concerning those relationships. Co-ordination of these compromises between the four case studies was overseen by my colleague Hilary Cowie, who is in effect scientific co-ordinator of EDPHiS and Editor-in-Chief of this set of reports.

We welcome comments and suggestions...

We welcome comments and suggestions on these Phase 1 reviews – on how they are useful, on what needs to be changed and on what in addition should be included – relative to their purpose within GPBH, which is to help ensure

that proposed policies and actions are informed by evidence. We hope you enjoy reading them, and please use the EDPHiS website to let us know what you think: www.edphis.org.

Meanwhile work is now ongoing on more detailed assessments, and on some cross-cutting issues (methodology; what states of the environment have wide impacts across several health endpoints; information needs), as part of the EDPHiS contribution to the Intelligence Partnership of GPBH; and we plan to complete and publish these in the coming months.

Fintan Hurley,
EDPHiS Principal Investigator
IOM Edinburgh, September 2010

CONTENTS

SUMMARY	7
1 Background	14
1.1 Asthma Definition	14
1.2 Context of Asthma	14
1.3 Current Government policy	15
2 Asthma DPSEEA Chains	16
2.1 Indoor Chains	16
2.2 Outdoor Chains	22
2.3 Particulate Matter Chains	25
2.4 Allergens and Other Chains	29
3 Priorities for further literature review	33
References	34

SUMMARY

Background

The Global Initiative for Asthma (GINA) defines asthma as a chronic inflammatory disorder of the airways that is associated with airway hyper-responsiveness leading to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. The episodes are often reversible either with treatment or spontaneously. The severity and frequency of these attacks varies from individual to individual.

Approximately 5.4 million people in the UK are currently receiving treatment for asthma according to the latest figures from Asthma UK. One in eleven children in the UK suffers from asthma (1.1 million). In Scotland in 2005, there were 390,000 people receiving treatment for asthma including 100,000 children. Data from the Information Services Division of NHS National Services Scotland (ISD) show that for children 14 and under consulting a physician for asthma was higher in males than in females during the year ending 31st March 2008. In all the other age groups the rate was higher for females than males with the exception of adults over the age of 75 where the rate was approximately the same for both genders. In addition, according to the Hospital Episode Statistics (HES), in England and Wales, over 20,000 children aged 0-14 were admitted to hospital for asthma between 2005 and 2006. Of those admitted, approximately 14,000 were males and 8,000 were females.

Socio-economic factors also influence the prevalence of asthma, as increased rates of asthma are associated with levels of deprivation which may be partly due to environmental tobacco smoke exposure. According to Asthma UK, a child is 1.5 times more likely to develop asthma if both of their parents smoke at home. In Scotland, approximately 40% of children are exposed to smoke at home.

The Scottish Government's 2009/10 HEAT targets (a core set of Ministerial objectives, targets and measures for the NHS) include a target for the treatment of asthma. The Government aims to achieve agreed reductions in the rates of hospital admissions and bed days of patients with asthma from 2006/07 to 2010/11.

In addition, poor air quality may lead to the exacerbation of asthma in children. Various Government policies have been put in place to control the emission of air pollutants in Scotland, the UK and throughout the European Union. The Scottish Government has set limit values for outdoor air concentrations of nitrogen dioxide, PM₁₀, and sulphur dioxide in addition to setting target values for ozone. Alert thresholds for nitrogen dioxide, ozone and sulphur dioxide have also been created by the government. In addition, to combat emissions from road traffic, Scotland has set up regulations for charging a fixed penalty to those with an emissions offence and for a stationary idling offence.

The European Union has set out Directives for emissions from both large combustion plants (SO₂, NO₂ and PM) and waste incinerators (SO₂ and NO₂). The UK has set out legislation to reduce emissions from large combustion plants and Scotland has set up legislation to limit the levels of emission from waste incinerators.

In Scotland, on the 26th of March 2006 a smoking ban in all public places came into effect, thereby eliminating environmental tobacco smoke in public places. The UK legislation on tobacco advertising and promotion and legislation on tobacco taxes would also have an effect on Environmental Tobacco Smoke (ETS). However, there is the possibility that the smoking ban may lead to more adults smoking in their homes, thereby increasing children's exposure to ETS.

In addition to the Governmental legislation that has gone into effect to reduce the level of air pollutants, the NHS has set up a guide of clinical standards for treating asthma in children and young adults – NHS Clinical Standards: Asthma services for children and young people.

DPSEEA maps

At the time of carrying out the scoping exercise, no DPSEEA mapping workshops had been held specifically addressing asthma, however some workshops addressing other health endpoints had also identified asthma as an outcome. In total, 10 DPSEEA chains were available from the DPSEEA mapping workshops primarily in relation to exposure to particulate matter from different sources. In addition, the EDPHiS asthma case study group put together a further 12 DPSEEA chains relevant to asthma as a health endpoint; and a second round of DPSEEA mapping workshops in relation to cardiovascular disease identified three further DPSEEA chains, 2 of which replicated those put together by the case study team. Chains which were put together by the case study team concentrated on the bottom half of the chain – from state to exposure to effect – and did not address drivers and pressures at this stage. Further DPSEEA workshops on asthma and air quality and on asthma and diet are due to be held in July 2009.

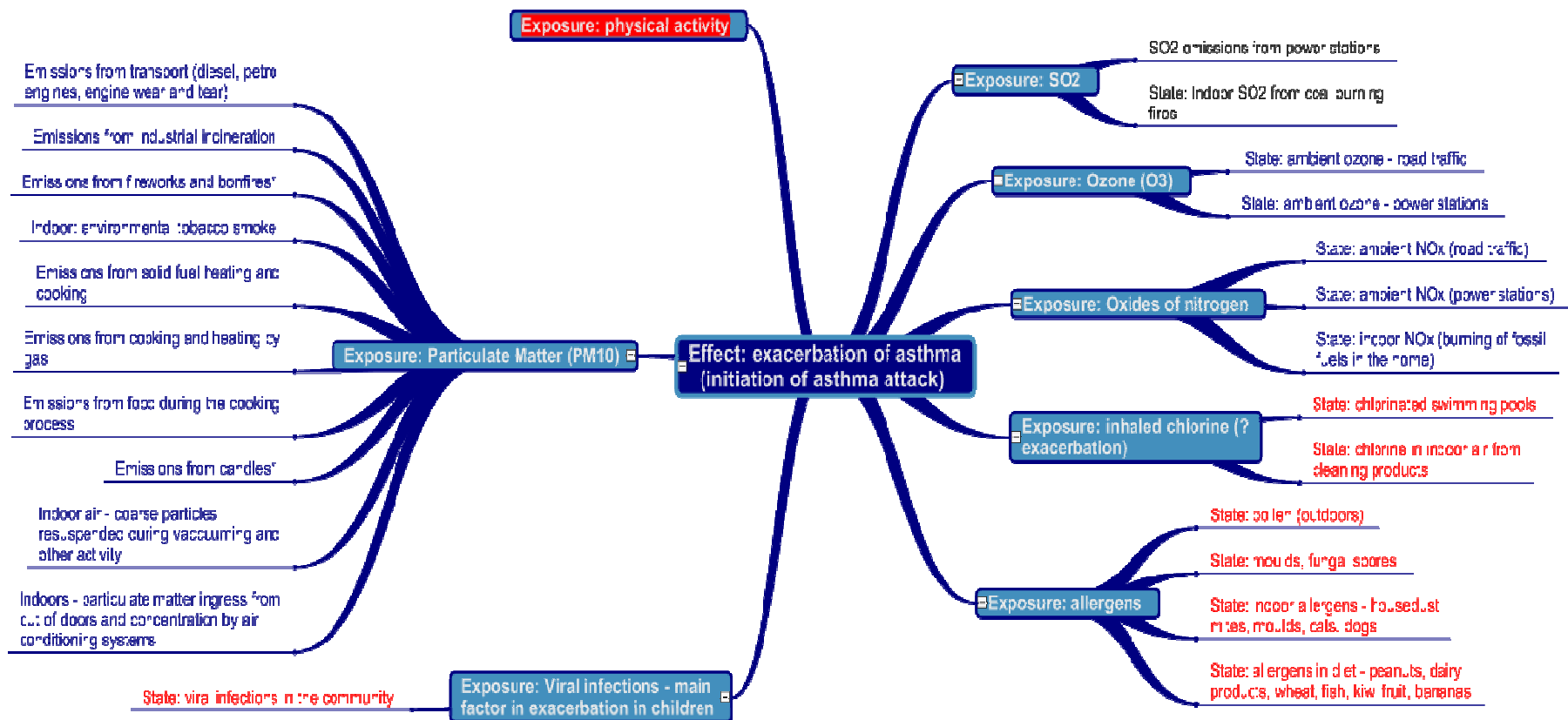
The 23 chains were broken down into 4 categories: Indoor Sources, Outdoor Sources, Particulate Matter (PM) whether indoor or outdoor, and Allergens and Other chains. Five of the chains were grouped into the indoor category and two were grouped into the outdoor. A further nine chains were grouped into the PM category and seven were grouped into the allergens and other category.

Chains related to the exacerbation of existing asthma are shown graphically in Figure 1 overleaf. In addition, the case study team identified four chains related to initiation or prevalence of asthma – maternal vitamin A intake during pregnancy, exposure to volatile organic compounds, inhaled pollen and allergens.

Figure 1: Asthma exacerbation: maps held by NHS Health Scotland or generated from state to effect by EDPHiS

Note, chains which are only roughly drafted have been indicated in red

Chains with an asterisk (*) have been identified by EDPHiS as having minimal impact on a population basis.



Summary of evidence

Indoor chains:

There is strong evidence that exposure to ETS, either as a child or *in utero*, causes respiratory problems, including asthma, in children. Several studies have shown that *in utero* exposure to parental smoking was associated with reduced lung function and respiratory problems in children. Maternal and parental smoking has also been found to be associated with an increased incidence of wheezing and increased prevalence of asthma. There is also strong evidence that ETS influences exacerbation of asthma and increased bronchial responsiveness in asthmatic children. ETS contains many chemical constituents, but it is not known which are responsible for asthma symptoms.

Evidence of a relationship between exposure to indoor NO₂ and asthma is inconsistent. It is likely that NO₂ does cause exacerbation of asthma in children; however the extent of the association is unclear. Human exposure studies of NO₂ only show adverse reactions at high (many hundreds of parts per billion) concentrations.

There are relatively few studies on the association between Volatile Organic Compound (VOC) exposure and asthma in children. However, one study in Australia found that most of the individual VOCs appeared to be significant risk factors for asthma, with the highest odds ratios for benzene followed by ethylbenzene and toluene.

The evidence available suggests that there may be an association between the use of indoor chlorinated swimming pools and levels of childhood asthma. Studies have found associations between asthma and cumulative pool attendance by children, swimming pool availability and acute exposure to chlorine in a swimming pool. These studies are however open to criticism as the markers of lung injury used are over-sensitive while the design of the epidemiological studies is also open to debate.

There are few studies on the effect of flame retardants and emissions from plastics on asthma in children. Several studies have suggested that emissions from phthalate plasticisers in various building materials and consumer products may cause respiratory problems in children.

Outdoor chains

There is good evidence that ozone is associated with exacerbation of asthma in children. The World Health Organisation (2009) estimate that 21,000 premature deaths per year are associated with ozone exceeding 70 ug/m³ (as a maximum daily 8 hour average) in EU25. Ozone is associated with 14,000 respiratory hospital admissions annually in EU25. Studies have shown that increases in ozone levels are associated with the increased use of asthma rescue medication, shortness of breath, and hospitalisations in children.

There is evidence that SO₂ exacerbates asthma in children, although it is difficult to separate the effects of SO₂ from other constituents of air pollution such as particulate matter (PM) and ozone. The UK Air Quality standard for SO₂ is based on human challenge responses to the gas in asthmatic individuals. The APHEA study (Air Pollution and Health: a European Approach), the largest epidemiological multi-centre study on asthma admissions in Europe, reported significant associations between daily values of SO₂ and the number of daily admissions for asthma in children. A later study found an association between increases of SO₂ and the daily number of admissions for asthma in children but could not differentiate whether these associations were due to SO₂ itself or to other pollutants such as PM₁₀ or CO.

Particulate Matter chains

Particulate matter (PM) is produced from a wide variety of sources. The DPSEEA chains in this category include emissions from: transport; industrial incineration; fireworks and bonfires; solid fuel heating and cooking; heating of hobs, grids and burners in cooking and heating; food during the cooking process; candles; vacuuming and activity within buildings (resuspension). While it is possible that the relationship between PM and health varies between types of particulate matter from different sources, current guidance is to use the same exposure-response function for PM from all sources.

There is strong evidence that PM is associated with the exacerbation of asthma. The World Health Organisation has found sufficient evidence to assume a causal relationship between exposure to air pollution and aggravation of asthma (mainly due to exposure to PM and ozone). There is evidence that PM-induced oxidative stress may be responsible for generating airway inflammation and airway hyper-reactivity that are both markers and possibly precursors for the development of asthma and studies have shown an association between paediatric emergency room visits for asthma and increased PM levels.

Allergens and other chains

Exposure to indoor allergens such as dust mites may not cause asthma directly; however in already allergic children, exposure to indoor allergens is associated with the development of asthma. There is evidence from intervention studies that a mite-free environment in infancy is associated with better lung function but more mite allergy among children at high risk for developing atopy. Associations are seen with different allergens in different populations, for example dust mites in the UK, and moulds (*altermeria*) and cockroach in the US. It is likely that the specific allergen is not that important, but that the response of the developing immune system to the most prevalent allergen in the environment is important.

Outdoor allergens such as pollens and moulds may exacerbate asthma. Several studies have found that allergens including grass pollen and fungal spores are associated with provocation or exacerbation of asthma attacks in

children resulting in visits to A&E departments and emergency hospital admissions.

Food allergy and asthma are both atopic diseases and therefore frequently co-exist. Food can induce bronchospasm and food allergy has been implicated as a risk factor for life-threatening asthma.

Upper respiratory tract infections and wheezing illnesses occur frequently in early childhood. Most viral infections associated with wheeze in infancy are attributable to respiratory syncytial virus, whereas in older children rhinovirus, influenza and parainfluenza virus are more common. A British study showed that in 80% of episodes in asthmatic children aged 9-11 years viruses could be detected in nasal aspirates which had been taken within 4 days of the wheezing attack. In most cases rhinovirus was identified. It has been suggested that viral infections early in life damage the growing lung or alter host immune regulation or that respiratory infections are more severe in infants and children with some underlying predisposition

The exact mechanism of exercise-induced asthma (EIA) is unknown, but there are two theories, and the mechanism may be a combination of the two. The first is the airway humidity theory, which suggests that air movement through the airway results in relative drying of the airway. This is believed to trigger a cascade of events that results in airway oedema secondary to hyperaemia (increased blood delivery) and increased perfusion in an attempt to combat the drying. The result is bronchospasm. The other theory is based on airway cooling and assumes that the air movement in the bronchial tree results in a decreased temperature of the bronchi, which may also trigger a hyperaemic response in an effort to heat the airway. Again, the result is a bronchospasm.

Exercise induced asthma (i.e. symptoms only when exercising) is extremely rare in children. Anecdotally, many schools stop children with asthma exercising maximally and some even get the children to warm up gradually before exercising maximally. Exercise is clearly related to obesity and should be encouraged in asthmatic children.

Recommendations for phase 2

In the next phase of the asthma case study, we will progress on several aspects, including:

- More detailed review of the particulate matter (PM) chains – including an assessment of which sources of PM are the most important. This will be done by looking at the levels of PM emitting from each source, the numbers of people potentially affected, and their distribution by factors including age, gender, socio-economic status and whether or not they have existing disease.
- Further investigation of the exposure-response (E-R) functions for PM, specifically a more detailed examination of more recent research into potentially different E-R functions for PM arising from different sources.

- Extension of the chains put together by the case study team to include drivers and pressures and a review of the evidence behind these. Inclusion and review of additional chains or revisions to existing chains arising from the DPSEEA workshops on asthma and air quality and asthma and diet being held over the summer 2009.
- Following the above, streamlining of the available chains to identify those for which the evidence is strongest and/or the health effects are largest.

1 Background

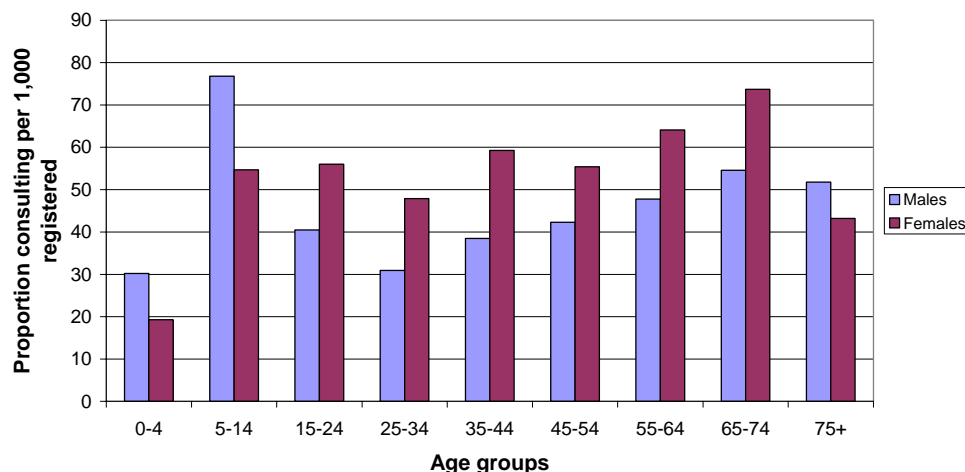
1.1 Asthma Definition

The Global Initiative for Asthma (GINA) defines asthma as a chronic inflammatory disorder of the airways that is associated with airway hyperresponsiveness leading to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. The episodes are often reversible either with treatment or spontaneously. The severity and frequency of these attacks varies from individual to individual.

1.2 Context of Asthma

Approximately 5.4 million people in the UK are currently receiving treatment for asthma according to the latest figures from Asthma UK. One in eleven children in the UK suffers from asthma (1.1 million). In Scotland in 2005, there were 390,000 people receiving treatment for asthma including 100,000 children. Data from the Information Services Division of NHS National Services Scotland (ISD) show that the number of children 14 and under consulting a physician for asthma was higher in males than in females during the year ending 31st March 2008. In all the other age groups the rate was higher for females than males with the exception of adults over the age of 75 where the rate was approximately the same for both genders.

Proportion of children consulting a physician for asthma in Scotland, 2007-2008



In addition, according to the Hospital Episode Statistics (HES), in England and Wales, over 20,000 children aged 0-14 were admitted to hospital for asthma between 2005 and 2006. Of those admitted, approximately 14,000 were males and 8,000 were females.

Socio-economic factors also influence the prevalence of asthma, as increased rates of asthma are associated with higher levels of deprivation which may be

partly due to environmental tobacco smoke exposure. According to Asthma UK, a child is 1.5 times more likely to develop asthma if both of their parents smoke at home. In Scotland, approximately 40% of children are exposed to smoke at home.

1.3 Current Government policy

The Scottish Government's 2009/10 HEAT targets (a core set of Ministerial objectives, targets and measures for the NHS) include a target for the treatment of asthma. The Government aims to achieve agreed reductions in the rates of hospital admissions and bed days of patients with asthma from 2006/07 to 2010/11.

In addition, poor air quality may lead to the exacerbation of asthma in children. Various Government policies have been put in place to control the emission of air pollutants in Scotland, the UK and throughout the European Union. The Scottish Government has set limit values for outdoor air concentrations of nitrogen dioxide, PM₁₀, and sulphur dioxide in addition to setting target values for ozone. Alert thresholds for nitrogen dioxide, ozone and sulphur dioxide have also been created by the government. In addition, to combat emissions from road traffic, Scotland has set up regulations for charging a fixed penalty to those with an emission offence and for a stationary idling offence.

The European Union has set out Directives for emissions from both large combustion plants (SO₂, NO₂ and PM) and waste incinerators (SO₂ and NO₂). The UK has set out legislation to reduce emissions from large combustion plants and Scotland has set up legislation to limit the levels of emissions from waste incinerators.

In Scotland, on the 26th of March 2006 a smoking ban in all public places came into effect, thereby eliminating environmental tobacco smoke in public places. This was followed by similar legislation in England, Wales and Northern Ireland. The UK legislation on tobacco advertising and promotion and legislation on tobacco taxes would also have an effect on Environmental Tobacco Smoke (ETS) exposure. However, there is the possibility that the smoking ban may lead to more adults smoking in their homes, thereby increasing children's exposure to ETS. However, a preliminary study conducted immediately after the Scottish legislation came into effect suggested that this was not happening.

In addition to the Governmental legislation that has gone into effect to reduce the level of air pollutants, the NHS has set up a guide of clinical standards for treating asthma in children and young adults – NHS Clinical Standards: Asthma services for children and young people

2 Asthma DPSEEA Chains

At the time of carrying out the scoping exercise, no DPSEEA mapping workshops had been held specifically addressing asthma, however some workshops addressing other health endpoints had also identified asthma as an outcome. In total, 10 DPSEEA chains were available from the DPSEEA mapping workshops primarily in relation to exposure to particulate matter from different sources. In addition, the EDPHiS asthma case study group put together a further 12 DPSEEA chains relevant to asthma as a health endpoint; a second round of DPSEEA mapping workshops in relation to cardiovascular disease identified three further DPSEEA chains, 2 of which replicated those put together by the case study team. Chains which were put together by the case study team concentrated on the bottom half of the chain – from state to exposure to effect with their concomitant actions – and did not address drivers and pressures at this stage. Further DPSEEA workshops on asthma and air quality and on asthma and diet were held in July 2009.

In this scoping report, the 23 identified chains are described and a high-level review of the level of evidence supporting them is provided. This review covers some key sources of evidence relevant to the chains, but does not include all available literature at this stage. A more detailed review of relevant chains will be done in phase 2 of the EDPHiS study.

With respect to air pollution the 23 chains were broken down into 4 categories: Indoor Sources, Outdoor Sources, Particulate Matter (PM) whether indoor or outdoor, and Allergens and Other chains. Five of the chains were grouped into the indoor category and two were grouped into the outdoor. A further nine chains were grouped into the PM category and seven were grouped into the allergens and other category.

2.1 Indoor Chains

2.1.1 Description of chains

The five chains included in the indoor category are Environmental Tobacco Smoke, NO₂, Volatile Organic Compounds, Chlorine and Emissions from plastics and flame retardants. These are summarised in Table 1. The environmental tobacco smoke chain was not grouped with the other particulate matter chains as most of the research on ETS examines the potential effects of ETS as a whole and not of its specific constituents. This approach would be too complex and the health based information supporting the approach would be limited. The levels of indoor NO₂ were seen as important because of exposures from gas fires, cookers and hobs. Volatile organic compounds are contained in many products in the indoor environment including cleaning agents, glues, floor coverings and dry cleaned clothes. Emissions of phthalates from plastics and from flame retardants are also increasing in the home with an increased reliance on plastic products and legislation on fire retardant materials.

2.1.2 Evidence review

I1: Environmental Tobacco Smoke (ETS)

There is strong evidence that exposure to ETS exacerbates asthma in children. There is strong evidence that exposure to ETS, either as a child or *in utero*, causes respiratory problems, including asthma, in children.

Numerous studies (e.g. DiFranza *et al* 2004, Gilliland *et al* 2000, Moshhammer *et al* 2006, Pattenden *et al* 2006) found that *in utero* exposure to parental smoking was associated with reduced lung function parameters or respiratory problems in children.

ETS exposure as a child also causes respiratory problems. Strachan and Cook (1998) found that maternal smoking was associated with an increased incidence of wheezing up to age 6, and found a pooled odds ratio of 1.37 (95% CI 1.15 to 1.64) for asthma prevalence if either parent smoked (data from 14 case-control studies). They also found that parental smoking is more strongly associated with wheezing among non-atopic children. Gilmour *et al* (2006) found evidence of a causal link between ETS exposure and the development of asthma in childhood.

Boldo (2007) found that exposure to ETS can increase the number of asthma episodes by an average of 6%. Gold (2000) evaluated the strength of evidence that ETS influences asthma exacerbation and found that data strongly supports the association of ETS with asthma severity and increased bronchial responsiveness in asthmatic children. Chilmonczyk (1993) also found that acute exacerbations of asthma increased with exposure.

ETS contains many constituents and it is not known which are responsible for asthma symptoms.

I2: NO₂ (indoor)

Evidence of the relationship between indoor NO₂ levels and asthma is inconsistent. It is likely that NO₂ does cause exacerbation of asthma in children; however the extent of the association is unclear.

A study in 2008 on 150 pre-school inner-city children in Baltimore, USA found that high indoor NO₂ concentrations were associated with increased asthma symptoms. Each 20ppb increase in NO₂ exposure was significantly associated with an increase in the number of days with limited speech, cough, and nocturnal symptoms (Hansel *et al* 2008). Belanger *et al* (2006) found that exposure to indoor NO₂ at levels well below the American Environmental Protection Agency outdoor standard (53 ppb as an annual mean) is associated with respiratory symptoms in asthmatic children.

Earlier studies (Melia *et al* 1982, Florey *et al* 1982, Florey *et al* 1979) found either no evidence of an association between NO₂ and respiratory illness, or only a weak association. Human exposure studies of NO₂ only show adverse

reactions at high (many hundreds of ppb) concentrations, with effects on bronchial responsiveness and no real effect on lung function except at extremely high (many ppm) concentrations, levels found only in exceptional occupational or accidental situations.

Tunncliffe *et al* 1994 showed that exposure to NO₂ (in combination with SO₂) at concentrations which can be found during episodes of increased outdoor and indoor air pollution, enhances the bronchoconstrictor effect of inhaled allergens in asthmatics.

13: Volatile Organic Compounds

There are few studies on the association between Volatile Organic Compound (VOC) exposure and asthma in children.

A study in Australia found that respiratory symptoms were related to measured VOC levels in classrooms. Most of the individual VOCs appeared to be significant risk factors for asthma, with the highest odds ratio for benzene followed by ethylbenzene and toluene. For every 10 unit increase in the concentration of toluene and benzene (mg/m³) the risk of having asthma increased by almost two and three times, respectively (Rumchev *et al* 2004).

14: Chlorine (indoor)

The evidence available suggests an association between the use of indoor chlorinated swimming pools and levels of childhood asthma.

Bernard *et al* (2006) found that cumulative pool attendance by children was one of the most consistent predictors of asthma, ranking immediately after atopy and a family history of asthma or hayfever.

Nickmilder and Bernard (2007) found that in children aged 6-7 years, the prevalence of ever having asthma increased with swimming pool availability.

Bonetto *et al* (2006) found that children acutely exposed to chlorine in a swimming pool presented lung function impairment.

These data are however open to criticism as the markers of lung injury used in these studies are over-sensitive while the design of the epidemiological studies is also open to debate.

15: Emissions from plastics and flame retardants

There are few studies on the effect of flame retardants and emissions from plastics on asthma in children. Several studies have suggested that emissions from phthalate plasticisers in various building materials and consumer products may cause respiratory problems in children.

One of the main sources for phthalate esters indoors is the plasticised polyvinyl chloride (PVC) materials (Bornehag *et al.* 2005) that are used in floor

and wall covering materials, shower curtains, adhesives, synthetic leather, toys, cosmetics, and many other consumer products. In the literature, the predominant phthalate described in indoor dust is di(2-ethylhexyl) phthalate (DEHP), typically observed in a concentration range of 0.01–10 mg/g.

Kolarik *et al* (2008) found a dose-response relationship between DEHP concentration and wheezing in Bulgarian pre-school children in the preceding 12 months. Bornehag *et al* (2004) found a dose response relationship between DEHP and asthma in children.

Table 1: EDPHiS asthma case study: details of chains on indoor exposure

Chain	Drivers	Pressures	State	Exposure	Effect	Contexts
I1. Environmental Tobacco Smoke	Tobacco control; Tobacco marketing; Corporate resources of tobacco industry; fiscal revenue to Treasury; peer pressure to smoke; smoking as a “right of passage” in young; reduction in buildings ventilation for energy efficiency	Emissions of tobacco smoke from lighted tobacco products and from exhaled breath of smokers within buildings and cars	Particulate matter (indoors)	Inhaled PM	Exacerbation of asthma	Increased susceptibility in those with existing health problems; behaviour (time spent indoors); Poor-quality housing/ventilation;
I2. NO₂		Emissions of NO ₂ from gas fires, gas cookers	Indoor levels of NO ₂	Inhaled NO ₂	Exacerbation of asthma	Age, behavioural (time spent indoors).
I3. Volatile Organic Compounds		Emissions of VOCs from cleaning agents, glues, resin, varnish, paint, carpets, caulks, floor coverings; air fresheners; dry cleaned clothes	VOC levels indoors	Inhaled VOCs	Initiation of asthma	Age, behavioural (time spent indoors).
I4. Chlorine			Chlorine levels in swimming pools; chlorine in cleaning products	Inhaled chlorine	Exacerbation of asthma	

I5. Emissions from plastics and flame retardants	Energy efficiency of buildings; fire retardant legislation; transport policy; reliance on plastics in home; consumerism; capitalism (imported goods)	Emissions of phthalates; Intentional or accidental inclusion in consumer products; use of more plastics; Emissions from flame retardants, compounded by low ventilation rates	Levels of phthalates, flame retardants in indoor air	Exposure to phthalates, flame retardants	Exacerbation of asthma	Age, behavioural (time spent indoors).
---	--	---	--	--	------------------------	--

2.2 Outdoor Chains

2.2.1 Description of chains

The two outdoor chains address exposure to Ozone and to Sulphur Dioxide. PM is excluded from this set of chains (see section 2.3 for PM chains).

2.2.2 Evidence review

O1: Ozone

There is good evidence that ozone is associated with exacerbation of asthma in children.

The World Health Organisation (2009) estimate that 21,000 premature deaths (all causes) per year are associated with ozone exceeding 70 $\mu\text{g}/\text{m}^3$ (as a maximum daily 8 hour average) in EU25 (the European Union had 25 member countries at the time of the study). Ozone is associated with 14,000 respiratory hospital admissions annually in EU25.

Studies have shown that increases in ozone levels are associated with the increased use of asthma rescue medication, shortness of breath, hospitalisations in children (e.g. Gent 2003, Lin 2008, Burnett 2001 and Mortimer 2002).

Lin (2008) found that the risk of hospital admissions in children increased 22% with a 1 ppb increase in mean ozone concentration. Moore (2008) estimated that hospital discharge rates in children increased 4.6% with a 10 ppb increase of ozone over the median level. However, not all studies show such an effect. For example, Lin (2003) found no association between ozone and asthma hospitalisation in children between the ages of 6 and 12.

O2: SO₂

There is evidence that SO₂ exacerbates asthma in children, however it is difficult to separate the effects of SO₂ from other constituents of air pollutions such as PM and ozone. However the UK Air Quality standard for SO₂ is based on human challenge responses to the gas in asthmatic individuals.

The APHEA study (Air Pollution and Health: a European Approach), the largest epidemiological multicentre study on asthma admissions in Europe, reported significant associations between daily values of SO₂ and the number of daily admissions for asthma in children (Sunyer *et al*, 1997). A later study (Sunyer, 2003) found that for an increase of 10 $\mu\text{g}/\text{m}^3$ of SO₂ the daily number of admissions for asthma in children increased 1.3%. The study could not differentiate whether these associations were due to SO₂ itself or to other pollutants such as PM₁₀ or CO.

Two recent studies suggested that SO₂ by itself might be related to respiratory diseases in children. In the Czech Republic and Poland, winter concentrations

of SO₂ were associated with wheezing and asthma prevalence diagnosed by a doctor (Pikhart *et al* 2001). In eastern Germany, decreases in levels of SO₂ were associated with a decrease of respiratory symptoms among children (Heinrich *et al* 2002).

Table 2: EDPHiS asthma case study: details of chains on outdoor exposure

Chain	Drivers	Pressures	State	Exposure	Effect	Contexts
O1. Ozone	Solvent industry; long distance transport; climate change	Hydrocarbon fuels – exhaust, refining, filling up cars	Ambient ozone levels	Ozone by inhalation	Exacerbation of asthma	Susceptibility – pre-existing ill health, geography – latitude and UV light, rural/urban differences, acclimatisation of populations to high levels
O2. SO₂	Energy policies, transport policies, shipping, trans-boundary issues – acid rain, agricultural practices	Emissions from coal fire energy production, road transport, domestic coal fires, diesel trains, shipping; SO ₂ drift from other countries	Elevated 24-hour mean SO ₂ ; Elevated 15-minute SO ₂ levels	SO ₂ by inhalation	Exacerbation of asthma	Proximity to ships, trains, industry; behaviour – exercise levels; synergistic effects with particulates of importance

2.3 Particulate Matter Chains

2.3.1 Description of chains

The nine chains included in the PM category (labelled as PM1 to PM9) are particulate matter from: transport; industrial incineration; fireworks and bonfires; solid fuel heating and cooking; heating of hobs, grids and burners in cooking and heating; food during the cooking process; candles; vacuuming and activity within buildings (resuspension); ingress of PM from outdoors.

2.3.2 Evidence review

PM1 to PM9: PM (indoor and outdoor)

Particulate matter is produced from a wide variety of sources. While it is possible that the relationship between PM and health varies between types of particulate matter from different sources, current guidance is to use the same exposure-response function for PM from all sources. In this scoping report we therefore review the evidence for an association between PM generally (regardless of specific source) and asthma. The possibility of different associations for PM from different sources will be examined in more detail in the second phase of the EDPHiS study.

There is strong evidence that PM is associated with the exacerbation of asthma. The World Health Organisation has found sufficient evidence to assume a causal relationship between exposure to air pollution and aggravation of asthma (mainly due to exposure to PM and ozone).

There is evidence that PM-induced oxidative stress may be responsible for generating airway inflammation and airway hyper-reactivity that are both markers and possibly precursors for the development of asthma (Gilmour *et al*, 2006).

Tolbert *et al* (2000) estimated a relative risk of paediatric emergency room visits for asthma for outdoor PM₁₀ of 1.04 per 15 ug/m³. Atkinson *et al* (2001) gave a summary PM₁₀ effect estimate (as a percentage change in mean number of daily respiratory admissions in children up to 14 years per 10 ug/m³ increase) of 1.2% for asthma.

McCormack *et al* (2009) studied indoor PM and found that in adjusted models, 10 ug/m³ increases in PM₁₀ and PM_{2.5} were associated with increased prevalence in asthmatic symptoms of 6% and 3% respectively.

Table 3: EDPHiS asthma case study: details of chains on indoor and outdoor exposure

Chain	Drivers	Pressures	State	Exposure	Effect	Contexts
PM1. PM from transport	Diesel powered trains; transport policies; car design; planning system; driving habits; cultural; commercial; economic/social; prioritisation of needs of car in spatial planning; social/family structure/work patterns; synchronisation of work day; urban design; poorly perceived public transport system; increasing distance travelled to perform basic functions of life; cost of housing leading to long commutes; fast lifestyles/changing work patterns	Emissions from diesel engines, petrol engines. Engine wear and tear – brake linings	PM (outdoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Exposure – behaviour, geographic; susceptibility – age, cumulative effects with other insults, underlying health status
PM2. PM from industrial incineration	Waste policy – reduced reliance on landfill driving use of incinerators	Emissions from incinerators	PM (outdoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Exposure – geographic; susceptibility – age, cumulative effects with other insults, underlying health status
PM3. PM from fireworks and bonfires	Cultural/social – bonfire night with fireworks	Emissions of PM10 from bonfires and fireworks – local and	PM (outdoor)	Inhaled PM	Exacerbation of asthma (respiratory	Exposure – geographic; susceptibility – age,

Chain	Drivers	Pressures	State	Exposure	Effect	Contexts
		hort periods of time			insult)	cumulative effects with other insults, underlying health status
PM4. Solid fuel heating and cooking	Fuel policy; poor maintenance and venting of appliances; building standards/planning guidance – hygrothermal conditions and level of ventilation; Commercial – product and servicing standards; air quality legislation – smokeless fuel regulations limited geographically; cultural/social influences – inappropriate use of solid fuel appliances	Solid fuel heating/cooking	PM (indoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Susceptibility – existing health problems, genetics; behaviour/function/age – time spent indoors; poor home maintenance; poor quality housing
PM5. Gas heating and cooking	Fuel policy; poor maintenance and venting of appliances; building standards/planning guidance – hygrothermal conditions and level of ventilation; cultural/social influences – inappropriate use of solid fuel appliances	Emissions from gas hobs and fires – emissions of PM from metal hobs, grids and burners	PM (indoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Susceptibility – existing health problems, genetics; behaviour/function/age – time spent indoors; poor home maintenance; cooking preferences; poor quality housing; smoking households

Chain	Drivers	Pressures	State	Exposure	Effect	Contexts
PM6. PM from food during cooking	Fuel policy; poor maintenance and venting of appliances; cultural – cooking preferences e.g. roasting/frying foods	Cooking – e.g. ultrafine particles from oil cooking – occupational exposure	PM (indoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Susceptibility – existing health problems, genetics, resilience; behaviour/function/age – time spent indoors; cooking preferences; poor quality housing
PM7. Candles as a source of PM indoors	Cultural/social influences use of candles indoors	Candles (but tends to be a source of larger particles)	PM (Indoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Susceptibility – existing health problems, genetics; behaviour/function/age – time spent indoors; poor quality housing
PM8. Vacuuming and activity within buildings (resuspension of coarse particles)		Vacuums and activity within building	PM (indoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Susceptibility – existing health problems, genetics; behaviour/function/age – time spent indoors; poor home maintenance – chimneys/boilers; poor quality housing
PM9. Ingress of PM from outdoors	See chains relating to ambient PM levels (I&O1-3); planning policies; climate change	Ingress of PM from outdoors; concentration of PM by air recycling/humidifiers in buildings close to major roads	PM (indoor)	Inhaled PM	Exacerbation of asthma (respiratory insult)	Susceptibility – existing health problems, genetics; behaviour/function/age – time spent indoors; poor quality housing

2.4 Allergens and Other Chains

2.4.1 Description of chains

The six allergen chains are Allergens (indoors), Allergens (Outdoors – mould), Allergens (outdoors – pollen), Allergens (diet) and Allergens (maternal diet). The two Other chains are Viral Infections (Rhinovirus) and Exercise.

2.4.2 Evidence review

A1: Allergens (indoor)

Exposure to indoor allergens such as dust mites may not cause asthma directly; however in already allergic children, exposure to indoor allergens is associated with the development of asthma.

There is evidence from intervention studies that a mite-free environment in infancy is associated with better lung function but, perhaps paradoxically, it is associated with a higher prevalence of mite allergy among children at high risk for developing atopy (Simpson et al, 2010)

Lau (2002) found no relationship between early indoor allergen exposure and the prevalence of asthma, wheeze and bronchial responsiveness. They found no data to support the hypothesis that exposure to allergens directly causes asthma. However, they did find that sensitisation to indoor allergens, such as mites and cats, was associated with asthma, wheeze and increased bronchial responsiveness. Gold (2000) found data to suggest that in already allergic populations, indoor allergen exposure could increase the risk of sensitisation to a specific allergen. In allergic populations, indoor allergen exposure may also increase the risk of the expression of asthma.

The most prevalent allergen differs according to location. The dust mite is a problem in the UK, moulds (*alternaria*) and cockroach allergens are a problem in the US, and cat allergens are a problem at altitude. However, it is likely that the specific allergen in itself is not very important. The more important factor in asthma will be the *response* of a child's developing immune system to the allergens in the environment.

A2 and A3: Allergens (outdoor)

Outdoor allergens such as pollens and moulds are known to exacerbate asthma. Further, Dales *et al* (2005) found that aeroallergens are an important cause of severe asthma morbidity in Canada.

Pollart *et al* (1988) reported that elevated IgE to grass allergens was associated with emergency room visits for asthma in California. Heguy (2008) found that emergency department visits increased with increasing concentrations of grass pollen in Canada.

Atkinson (2006) found that fungal spore concentrations may provoke or exacerbate asthma attacks in children resulting in visits to A&E departments and emergency hospital admissions and was responsible for a greater effect than contemporaneous exposure to air pollutants.

A4 and A5: Allergens (diet)

Food allergy and asthma are both atopic diseases and therefore frequently co-exist. Food can induce bronchospasm and food allergy has been implicated as a risk factor for life-threatening asthma (Roberts *et al*, 2003 and Wang *et al*, 2005).

A6: Viral infections (rhinovirus)

Lau *et al* (2002) found that children with 2 or more episodes of runny nose before the age of 1 year were less likely to develop asthma by the age of 7. Wright (2002) found that some of the risk factors for early LRIs, such as exposure to other children in infancy, appear to be associated with protection from later allergic wheezing. Wright also found that early LRIs are markers of increased risk, rather than causes.

A7: Exercise

The exact mechanism of exercise-induced asthma (EIA) is unknown, but there are two theories, and the mechanism may be a combination of the two.

The first is the airway humidity theory, which suggests that air movement through the airway results in relative drying of the airway. This is believed to trigger a cascade of events that results in airway oedema secondary to hyperaemia (increased blood delivery) and increased perfusion in an attempt to combat the drying. The result is acute airway narrowing.

The other theory is based on airway cooling and assumes that the air movement in the bronchial tree results in a decreased temperature of the bronchi, which may also trigger a hyperaemic response in an effort to heat the airway.

EIA (i.e. symptoms only when exercising) is extremely rare in children. Anecdotally, many schools stop children with asthma exercising maximally and some even get the children to warm up gradually before exercising maximally. Exercise is clearly related to obesity and should be encouraged in asthmatic children.

Table 4: EDPHiS asthma case study: details of non-spatial chains

Chain	Drivers	Pressures	State	Exposure	Effect	Contexts
A1. Allergens (indoors) – dust mites, mould, pets			Allergen levels	Inhalation	Exacerbation and initiation of asthma	Socio-economic factors. Humidity and other environmental conditions
A2. Allergens (outdoors) – mould			Mould levels	Inhaled fungal spores	Exacerbation of asthma	Seasonality
A3. Allergens (outdoors) - pollen			Pollen levels	Inhaled pollen	Exacerbation of asthma. Causation is probably linked to a small time window of a few weeks	Seasonality, thunderstorms
A4. Allergens (in diet) - maternal	Vitamin E is not an allergen, it is a dietary exposure			Vitamin E and ?D intake during pregnancy	Causation	
A5. Allergens (in diet)			Availability of products	Dietary intake	Exacerbation of asthma	

A6. Viral infections (rhinovirus)			Viral infections exist within the community	Inhaled route	Main factor in exacerbation of asthma	
A7. Exercise			Opportunities for exercise	Amount of exercise taken	Exacerbation of asthma	This chain seems to imply less exercise, less asthma which is wrong

3 Priorities for further literature review

- include a more detailed review of PM chains including the possibility of different Exposure Response Functions for PM from different sources
- review of drivers/pressures
- identify quantifiable Exposure Response Functions
- exclude non-important chains e.g. bonfires, fireworks, candles etc
- identify further studies to support each chain.

References

- Amann, M., Derwent, D., Forsberg, B., Hänninen, O., Hurley, F., Krzyzanowski, M., et al. (2008). *Health risks of ozone from long-range transboundary air pollution* WHO Regional Office for Europe.
- Atkinson, R. W., Anderson, H. R., Sunyer, J., Ayres, J., Baccini, M., Vonk, J. M., et al. (2001). Acute effects of particulate air pollution on respiratory admissions: Results from APHEA 2 project. *air pollution and health: A european approach. American Journal of Respiratory and Critical Care Medicine*, 164(10 Pt 1), 1860-1866.
- Atkinson, R. W., Strachan, D. P., Anderson, H. R., Hajat, S., & Emberlin, J. (2006). Temporal associations between daily counts of fungal spores and asthma exacerbations. *Occupational and Environmental Medicine*, 63(9), 580-590.
- Belanger, K., Gent, J. F., Triche, E. W., Bracken, M. B., & Leaderer, B. P. (2006). Association of indoor nitrogen dioxide exposure with respiratory symptoms in children with asthma. *American Journal of Respiratory and Critical Care Medicine*, 173(3), 297-303.
- Bernard, A., Carbonnelle, S., de Burbure, C., Michel, O., & Nickmilder, M. (2006). Chlorinated pool attendance, atopy, and the risk of asthma during childhood. *Environmental Health Perspectives*, 114(10), 1567-1573.
- Boldo, E. (2007). *Feasibility of health impact assessment in european children exposed to environmental tobacco smoke (ETS)* The European Environment and Health Information System (ENHIS).
- Bonetto, G., Corradi, M., Carraro, S., Zanconato, S., Alinovi, R., Folesani, G., et al. (2006). Longitudinal monitoring of lung injury in children after acute chlorine exposure in a swimming pool. *American Journal of Respiratory and Critical Care Medicine*, 174(5), 545-549.
- Bornehag, C. G., Lundgren, B., Weschler, C. J., Sigsgaard, T., Hagerhed-Engman, L., & Sundell, J. (2005). Phthalates in indoor dust and their association with building characteristics. *Environmental Health Perspectives*, 113(10), 1399-1404.
- Bornehag, C. G., Sundell, J., Weschler, C. J., Sigsgaard, T., Lundgren, B., Hasselgren, M., et al. (2004). The association between asthma and allergic symptoms in children and phthalates in house dust: A nested case-control study. *Environmental Health Perspectives*, 112(14), 1393-1397.
- Burnett, R. T., Smith-Doiron, M., Stieb, D., Raizenne, M. E., Brook, J. R., Dales, R. E., et al. (2001). Association between ozone and hospitalization for acute respiratory diseases in children less than 2 years of age. *American Journal of Epidemiology*, 153(5), 444-452.

Cakmak, S., Dales, R. E., Judek, S., & Coates, F. (2005). Does socio-demographic status influence the effect of pollens and molds on hospitalization for asthma? results from a time-series study in 10 canadian cities. *Annals of Epidemiology*, 15(3), 214-218.

Chilmonczyk, B. A., Salmun, L. M., Megathlin, K. N., Neveux, L. M., Palomaki, G. E., Knight, G. J., et al. (1993). Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *The New England Journal of Medicine*, 328(23), 1665-1669.

DiFranza, J. R., Aligne, C. A., & Weitzman, M. (2004). Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics*, 113(4 Suppl), 1007-1015.

<http://emedicine.medscape.com/article/88849-overview>

Florey Cdu, V., Melia, R., Goldstein, B., Morris, R., John, H. H., & Clark, D. (1982). The epidemiology of indoor nitrogen dioxide in the U.K. *Schriftenreihe Des Vereins Fur Wasser-, Boden- Und Lufthygiene*, 53, 209-218.

Florey, C. V., Melia, R. J., Chinn, S., Goldstein, B. D., Brooks, A. G., John, H. H., et al. (1979). The relation between respiratory illness in primary schoolchildren and the use of gas for cooking--III. nitrogen dioxide, respiratory illness and lung infection. *International Journal of Epidemiology*, 8(4), 347-353.

Gent, J. F., Triche, E. W., Holford, T. R., Belanger, K., Bracken, M. B., Beckett, W. S., et al. (2003). Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA : The Journal of the American Medical Association*, 290(14), 1859-1867.

Gilliland, F. D., Berhane, K., McConnell, R., Gauderman, W. J., Vora, H., Rappaport, E. B., et al. (2000). Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax*, 55(4), 271-276.

Gilmour, M. I., Jaakkola, M. S., London, S. J., Nel, A. E., & Rogers, C. A. (2006). How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environmental Health Perspectives*, 114(4), 627-633.

Gilmour, M. I., Jaakkola, M. S., London, S. J., Nel, A. E., & Rogers, C. A. (2006). How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environmental Health Perspectives*, 114(4), 627-633.

Gold, D. R. (2000). Environmental tobacco smoke, indoor allergens, and childhood asthma. *Environmental Health Perspectives*, 108 Suppl 4, 643-651.

- Hansel, N. N., Breyse, P. N., McCormack, M. C., Matsui, E. C., Curtin-Brosnan, J., Williams, D. L., et al. (2008). A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environmental Health Perspectives*, 116(10), 1428-1432.
- Heguy, L., Garneau, M., Goldberg, M. S., Raphoz, M., Guay, F., & Valois, M. F. (2008). Associations between grass and weed pollen and emergency department visits for asthma among children in montreal. *Environmental Research*, 106(2), 203-211.
- Heinrich, J., Hoelscher, B., Frye, C., Meyer, I., Pitz, M., Cyrus, J., et al. (2002). Improved air quality in reunified germany and decreases in respiratory symptoms. *Epidemiology (Cambridge, Mass.)*, 13(4), 394-401.
- Kolarik, B., Naydenov, K., Larsson, M., Bornehag, C. G., & Sundell, J. (2008). The association between phthalates in dust and allergic diseases among bulgarian children. *Environmental Health Perspectives*, 116(1), 98-103.
- Lau, S., Nickel, R., Niggemann, B., Gruber, C., Sommerfeld, C., Illi, S., et al. (2002). The development of childhood asthma: Lessons from the german multicentre allergy study (MAS). *Paediatric Respiratory Reviews*, 3(3), 265-272.
- Lin, M., Chen, Y., Burnett, R. T., Villeneuve, P. J., & Krewski, D. (2003). Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: A bi-directional case-crossover analysis. *Journal of Epidemiology and Community Health*, 57(1), 50-55.
- Lin, S., Liu, X., Le, L. H., & Hwang, S. A. (2008). Chronic exposure to ambient ozone and asthma hospital admissions among children. *Environmental Health Perspectives*, 116(12), 1725-1730.
- McCormack, M. C., Breyse, P. N., Matsui, E. C., Hansel, N. N., Williams, D., Curtin-Brosnan, J., et al. (2009). In-home particle concentrations and childhood asthma morbidity. *Environmental Health Perspectives*, 117(2), 294-298.
- Melia, R. J., Florey Cdu, V., Morris, R. W., Goldstein, B. D., John, H. H., Clark, D., et al. (1982). Childhood respiratory illness and the home environment. II. association between respiratory illness and nitrogen dioxide, temperature and relative humidity. *International Journal of Epidemiology*, 11(2), 164-169.
- Moore, K., Neugebauer, R., Lurmann, F., Hall, J., Brajer, V., Alcorn, S., et al. (2008). Ambient ozone concentrations cause increased hospitalizations for asthma in children: An 18-year study in southern california. *Environmental Health Perspectives*, 116(8), 1063-1070.
- Mortimer, K. M., Neas, L. M., Dockery, D. W., Redline, S., & Tager, I. B. (2002). The effect of air pollution on inner-city children with asthma. *The*

European Respiratory Journal : Official Journal of the European Society for Clinical Respiratory Physiology, 19(4), 699-705.

Moshhammer, H., Hoek, G., Luttmann-Gibson, H., Neuberger, M. A., Antova, T., Gehring, U., et al. (2006). Parental smoking and lung function in children: An international study. *American Journal of Respiratory and Critical Care Medicine*, 173(11), 1255-1263.

Netdoctor - http://www.netdoctor.co.uk/diseases/facts/asthma_extentinuk.htm

Nickmilder, M., & Bernard, A. (2007). Ecological association between childhood asthma and availability of indoor chlorinated swimming pools in europe. *Occupational and Environmental Medicine*, 64(1), 37-46.

Pattenden, S., Antova, T., Neuberger, M., Nikiforov, B., De Sario, M., Grize, L., et al. (2006). Parental smoking and children's respiratory health: Independent effects of prenatal and postnatal exposure. *Tobacco Control*, 15(4), 294-301.

Pikhart, H., Bobak, M., Gorynski, P., Wojtyniak, B., Danova, J., Celko, M. A., et al. (2001). Outdoor sulphur dioxide and respiratory symptoms in czech and polish school children: A small-area study (SAVIAH). small-area variation in air pollution and health. *International Archives of Occupational and Environmental Health*, 74(8), 574-578.

Pollart, S. M., Reid, M. J., Fling, J. A., Chapman, M. D., & Platts-Mills, T. A. (1988). Epidemiology of emergency room asthma in northern california: Association with IgE antibody to ryegrass pollen. *The Journal of Allergy and Clinical Immunology*, 82(2), 224-230.

Roberts, G., Patel, N., Levi-Schaffer, F., Habibi, P., & Lack, G. (2003). Food allergy as a risk factor for life-threatening asthma in childhood: A case-controlled study. *The Journal of Allergy and Clinical Immunology*, 112(1), 168-174.

Rumchev, K., Spickett, J., Bulsara, M., Phillips, M., & Stick, S. (2004). Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax*, 59(9), 746-751.

Simpson, A., Tan, V.Y., Winn, J., Svensen, M., Bishop, C.M., Heckerman, D.E., Buchan, I., Custovic, A. (2010). Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *American journal of respiratory and critical care medicine*, 181(11), 1200-1206.

Strachan, D. P., & Cook, D. G. (1998). Health effects of passive smoking. 6. parental smoking and childhood asthma: Longitudinal and case-control studies. *Thorax*, 53(3), 204-212.

Sunyer, J., Atkinson, R., Ballester, F., Le Tertre, A., Ayres, J. G., Forastiere, F., et al. (2003). Respiratory effects of sulphur dioxide: A hierarchical multicity

analysis in the APHEA 2 study. *Occupational and Environmental Medicine*, 60(8), e2.

Sunyer, J., Spix, C., Quenel, P., Ponce-de-Leon, A., Ponka, A., Barumandzadeh, T., et al. (1997). Urban air pollution and emergency admissions for asthma in four european cities: The APHEA project. *Thorax*, 52(9), 760-765.

Tolbert, P. E., Mulholland, J. A., MacIntosh, D. L., Xu, F., Daniels, D., Devine, O. J., et al. (2000). Air quality and pediatric emergency room visits for asthma in atlanta, georgia, USA. *American Journal of Epidemiology*, 151(8), 798-810.

Tunnicliffe, W. S., Burge, P. S., & Ayres, J. G. (1994). Effect of domestic concentrations of nitrogen dioxide on airway responses to inhaled allergen in asthmatic patients. *Lancet*, 344(8939-8940), 1733-1736.

Wang, J., Visness, C. M., & Sampson, H. A. (2005). Food allergen sensitization in inner-city children with asthma. *The Journal of Allergy and Clinical Immunology*, 115(5), 1076-1080.

World Health Organisation. (2005). *Effects of air pollution on children's health and development - a review of the evidence*.

Wright, A. L. (2002). Epidemiology of asthma and recurrent wheeze in childhood. *Clinical Reviews in Allergy & Immunology*, 22(1), 33-44.