Institute for Environment and Health

A review of potential causative factors for asthma

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1 Introduction[1]

1.1 Aims and objectives

The purpose of this report is to review the recent literature (from 1998) regarding factors influencing the development of asthma in a previously symptom-free individual. Onset of asthma in childhood, adolescence and adulthood are considered. It is important to note that this report is not a 'systematic review' of recent literature on causes of asthma, and a good deal of individual judgement has been used in selection of papers. The aim is to bring together a wide variety of theories on asthma causation into one document, as most published reviews on this subject concentrate on a specific theme rather than the full range of hypotheses implicated in asthma causation. No attempt has been made to analyse the methodology of each study critically; the particular theory or theme for investigation has been considered the important feature of the study, rather than the quality or weight of the evidence supporting that theory.

Essentially therefore, this report is a subjective investigation into the principal factors that may be involved in the onset of asthma, but it is hoped that the work will also throw up useful insights and highlight areas worthy of further research.

1.2 Defining asthma

As pointed out by Tattersfield *et al.* (2002), there is no standard definition of asthma. For the purposes of this report the following working definition of asthma has been adopted: reversible obstruction of airways due to bronchial hyperreactivity, associated with inflammation and oedema of the airways. It is important to bear in mind that clinical diagnosis of asthma may vary between countries, time periods, and even between clinicians. Despite this lack of standardisation, the clinical diagnosis of asthma in young adults is a repeatable finding in populations with developed health services (Tattersfield *et al.*, 2002).

In Western societies, the development of asthma usually requires development of allergy, localisation of the allergic inflammatory response to the lung and the development of bronchial hyperreactivity (Gold, 2000). A diagrammatic representation of the course of development and progression of asthma in an individual is given in Figure 1.

1.3 Influencing factors

This paper does not consider the genetic or hereditary factors associated with asthma. It is assumed that an asthmatic individual has an innate predisposition to asthma at the genetic level, which is then impacted by external factors to result in the individual experiencing the symptoms of asthma. The focus of this paper is on the external factors that may bring about the onset of asthma in a susceptible individual. Specific pathophysiological and immunological mechanisms are not discussed in detail. The factors of main concern are those that are associated with the individual's environment, both physical and social. These factors include:

- factors related to outdoor air pollution;
- indoor environment;
- 'hygiene' and related factors;

[1] For references marked with an asterisk, only the abstract was reviewed

- maternal and birth factors;
- drug related factors;
- dietary factors; and
- body factors.

There are also various factors that do not fit clearly into any of the above categories.

Factors that exacerbate asthma in an individual previously diagnosed as suffering from the condition are not discussed here. Specific factors related to occupational exposures are not considered, as the focus of the report is on factors that may affect the general population. Initially it was hoped to include only those studies that have as a measured outcome variable the presence of asthma diagnosed by a health professional, but many of the studies were found to have been based on self-reported questionnaires that did not stipulate whether a positive response to having asthma should be based on having a doctor's diagnosis. Hence it was decided to include the latter studies also, to avoid excluding potentially relevant information. Studies that report on other factors that may or may not be related to current presence or future development of asthma, for example recurrent wheeze, lung function tests, skin prick tests, atopy/allergy in general or other atopic conditions such as eczema or hay fever, have been excluded.

A particular issue addressed by this report is the role of air pollution in bringing about asthma in previously symptom-free individuals, either in isolation or acting in combination with other environmental factors.

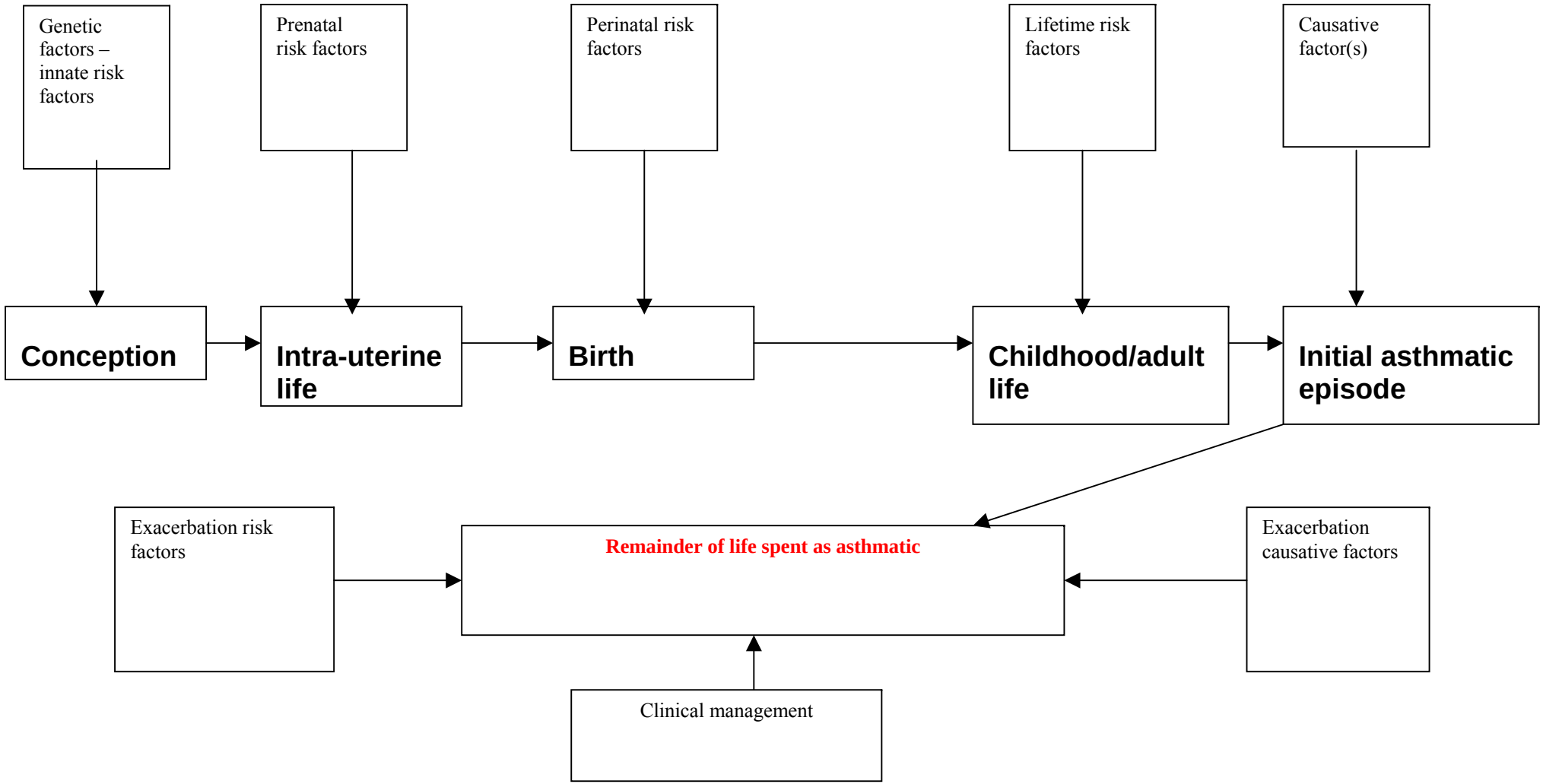
1.4 Methodology

The methodology involved an initial search using MEDLINE® and EMBASE®, with descriptors for asthma and subheadings for aetiology. This search strategy identified over 2000 references, both reviews and primary sources. To reduce the number of references, while still covering the main themes in asthma causation identified by this search strategy, a selection of abstracts for both reviews and primary papers was downloaded; this was then used to make the final selection of entire papers to be obtained. From approximately 800 abstracts downloaded, about 20 recently published reviews were selected. It was anticipated that these overviews would provide an indication of current views and ideas on the causation of asthma, as well as suitable primary references for further detail. In a+ddition, approximately 30 primary papers were obtained, based on the initial search, plus papers discovered from reviews. The selection of papers for further investigation was by individual judgement according to the subject matter of the paper and its contribution to the theme of interest. Abstracts for papers that appeared to be of value, but were not selected to be obtained in full, have also been summarised, to avoid unnecessarily restricting the scope of the report. Where this has been done, there is a clear indication in the text and bibliography. It should be borne in mind that the studies selected for inclusion in this report do not necessarily represent the extensive current literature on asthma.

1.5 Geographical variations

The recent European Community Respiratory Health Survey (ECRHS) aimed to assess geographical variation in asthma among adults. In a published review of this extensive cross-sectional survey, investigating connections between asthma and a wide variety of potential causal factors, data from approximately 140 000 individuals from 22 countries were presented (Janson *et al.*, 2003). In this study, the incidence of asthma was found to be highest in Australia, New Zealand, USA, Ireland and the UK. Low incidences were found in Iceland, parts of Spain, Germany, Italy, Algeria and India. Overall, the ECRHS demonstrated large geographical differences in the prevalence of asthma, with higher rates in English-speaking countries, and lower rates in Mediterranean countries and Eastern Europe. The geographical pattern of asthma was consistent with the pattern of atopy and bronchial hyperresponsiveness, suggesting that the geographical variations in asthma prevalence are genuine and caused by environmental factors.

Figure 1 Timeline indicating the progression of asthma in the individual, from conception, through birth and beyond, to the event of their first asthmatic episode and their subsequent lifespan as an asthmatic



2 Specific themes in asthma causation[2]

2.1 Outdoor air pollution

Reporting the work of others, Stone (2000) mentions a cross-sectional study in Holland, which discovered significantly more doctor-diagnosed asthma in children within 100 m of a freeway than in other children. Stone (2000) goes on to comment that in general it appeared that particulate matter with a mass median aerodynamic diameter less than 10 μm (PM_{10}) was not a primary cause of asthma, despite its ability to induce inflammation of the airways and exacerbate pre-existing inflammation (also citing from earlier work). In another review, Peden (2000) states that there is no clear indication that ozone, sulphur dioxide or nitrogen dioxide have any role in asthma pathogenesis or induction of atopy.

Supporting the hypothesis of an association between asthma and exposure to outdoor particulate air pollution is a study from California, cited in a review by Strachan (2000). This study, among Seventh Day Adventists, found that the onset of asthma in adulthood (diagnosed by a physician) was significantly and positively associated with cumulative outdoor exposure to particulate air pollution. Ambient particle concentrations were highly correlated with ozone levels, so it was not possible to determine the roles played independently by each pollutant.

Another review of epidemiological evidence looks at outdoor air pollutant exposures in relation to onset of asthma (Delfino, 2002). The difficulties of understanding any potential causal factors in air pollution, due to the many aetiological factors of asthma and to the complexity of air pollution exposures, are acknowledged. Delfino (2002) also reports on the work of previous authors on the cohort study of Seventh Day Adventists in California where subjects were followed up for at least 10 years. An association was found between development of asthma and outdoor concentrations of total suspended particulates and total suspended sulphates. A similar association was found, in males only, between asthma and ozone, possibly because males in the study spent more time outdoors than females).

In the same review, Delfino (2002) turns his attention to traffic-related exposures and asthma. He reports on several studies that have shown associations between traffic exposures and asthma prevalence. Pollutants found to be positively associated ($p < 0.001$) with physician diagnosed asthma in boys and girls in a study in Taiwan were carbon monoxide and nitrogen oxides; in this study no association was observed between asthma prevalence and sulphur dioxide or PM_{10} (apart from an unexpected negative association between asthma in boys and PM_{10}). In a study based in Dresden, Germany, only benzene was found to be significantly associated with an increased prevalence of asthma. (It is possible that the traffic pollutants mentioned above may not be directly related to asthma prevalence, but may be acting as a marker for other traffic pollutants that do have a direct association.)

In considering the role of polyaromatic hydrocarbons (PAHs), Delfino (2002) considers that there is experimental evidence to support a role for PAHs in the onset of asthma. Epidemiological studies that showed an association between childhood asthma and environmental tobacco smoke (ETS) may in part be highlighting an effect of PAHs, as may studies revealing a significant relationship between asthma and traffic-related exposure.

Overall, Delfino's review (2002) supports the view that asthma and atopy are higher among people living near heavy traffic. Evidence from studies showing a higher proportion of asthma in more

[2] For references marked with an asterisk, only the abstract was reviewed

developed countries, and in urban rather than rural areas, generally supports this view. Studies in Africa (as cited in Delfino, 2002) have indicated a higher prevalence of asthma in children in urban than in rural areas, and that the discrepancy has narrowed as rural areas have become more Westernised. However, not all studies show this clearcut urban–rural difference, making interpretation of causation difficult. A possible alternative explanation for any urban increase in asthma prevalence is a potential protective effect of farm-based lifestyles among rural children.

A study by Korean authors (Kim *et al.*, 2001) aimed to identify any relationship between exposure to industrial outdoor pollutants and asthma in children. This was a large cross-sectional study involving 7511 children aged 7–12 years. Subjects resided either in a heavily polluted industrial area or in a less polluted neighbouring area. A questionnaire survey asked about asthma and other conditions such as rhinitis and eczema. Skin-prick tests and bronchial provocation tests were also used. The questionnaire assessed asthma status by ever experiencing wheeze and wheeze within last 12 months. By this metric, the prevalence of asthma was significantly higher in the more polluted area than in the less polluted area. The rate of positive bronchial provocation tests was also higher in the children from the heavily polluted area than in controls. However, there were no significant differences between the two areas in prevalence of atopy as measured by the skin-prick tests. Scant data on exposure to specific air pollutants were provided, but it was noted that mean concentrations of sulphur dioxide and nitrogen dioxide exceeded WHO standards in the industrialised area, and were much lower in the non-industrial area. The authors concluded that outdoor air pollutants from industry may play a role in development and/or exacerbation of asthma in exposed individuals by enhancing bronchial responsiveness. However, their use of self-reporting questionnaires regarding the symptom of wheeze to determine asthmatic status, rather than using a health professional diagnosis, may have led to unreliable results.

Another study based in Taiwan looked at the prevalence rates of asthma among children mainly aged 13–15 years (Lin *et al.*, 2001). This study took the form of a mass screening survey of over 86 000 subjects. Information about asthma was drawn from a survey using a questionnaire that included a section for parents and a section for the child. The parental section included questions about physician diagnosis of asthma, as well as the child's symptoms. When looking at asthma prevalence in relation to urbanisation, the prevalence was highest in the highly urbanised areas, followed by the moderately urbanised areas, with the lowest prevalence in the less urbanised/rural areas. A comparison of asthma prevalence in relation to carbon monoxide was also made. The baseline for comparison of odds ratios (ORs), that is an OR of 1, was a carbon monoxide level of < 0.75 ppm. Carbon monoxide in the range of 0.75–0.99 ppm had an adjusted OR of 1.10 (95% CI 1.03–1.16). At the highest level of carbon monoxide, ≥ 1.0 ppm, the OR was 1.30 (95% CI 1.18–1.42). Factors adjusted for included sex, school grade, passive smoking, incense burning in the home, exercise and parental education. A further comparison was made between asthma prevalence and level of air pollution as ranked by the parents. There was a progressively higher OR for asthma (as compared with the OR for no air pollution) in each of three categories: light, moderate and heavy pollution. Each of these categories had a significantly higher OR (adjusted for the same factors as the carbon monoxide comparison) than the 'no pollution' category. However, the categories were based on the parental ranking of air pollution and hence may not be accurately related to the actual levels of any pollutant. Overall, this study provides some indication that prevalence of asthma is linked to air pollution levels in Taiwan, but more detailed studies with more objective criteria for both determination of asthma status in individuals and exposure levels would be required for any firm conclusion to be drawn.

A further large survey from Taiwan (Wang *et al.*, 1999) used a similar methodology for data gathering. This survey included over 160 000 subjects aged 11–15 years from two areas of Taiwan. Both indoor and outdoor air pollutants were investigated in relation to asthma prevalence. Among outdoor air pollutants, those associated with significantly (the $p < 0.01$) increased prevalence of asthma were total suspended particulates (≥ 181 $\mu g/m^3$), sulphur dioxide (≥ 0.013 ppm), nitrogen dioxide (≥ 0.028 ppm), carbon monoxide (≥ 0.80 ppm), ozone (≥ 0.022 ppm), and airborne dust particles (≥ 7.6 ton/km^2/month). Interestingly, PM_{10} concentration had an association with lower asthma prevalence (OR 0.95, 95% CI 0.91–0.99).

An interesting study compared prevalences of asthma (as well as other atopic conditions) in two arctic regions, one in Norway and the other in Russia (Dotterud *et al.*, 2000). Two cross-sectional surveys were conducted. The Norwegian survey comprised 1102 adults and was performed in 1991. The Russian study included 3368 adults and was conducted in 1994. The determination of rates of disease was by self-administered questionnaire, whereby the respondents were asked for details of symptoms of a particular condition (as opposed to having received a diagnosis from a physician). There was no significant difference in the prevalence of asthma in the two regions, whereas both eczema and allergic rhinoconjunctivitis were more prevalent in the Norwegian area than in the Russian area. Outdoor air pollution, including sulphur dioxide, particulates and heavy metals, was higher in the Russian area than the Norwegian area. Neither area had heavy traffic or outdoor levels of nitrogen dioxide. Hence, this study indicates that outdoor air pollution is not a major determinant of asthma in adults.

A comparison between prevalences of asthma among 14–17 year old school students in Canada and the Czech Republic was conducted by Vacek (1999). In this study, a cohort of 430 students from Vancouver, Canada and 219 students from Prague, Czech Republic were compared. A questionnaire to the students asked about details of history of asthma and allergy. A history of asthma or chronic cough was reported by 9.5% of the Canadian students and 14.5% of the Czech students. The proportion of students with recent use of asthma medication was 5.3% in the Canadians and 4.1% in the Czechs. There were no significant differences in the values between the two groups, nor was there any significant difference in the levels of reported personal history of allergy (12.9% in the Canadians, 25.6% in the Czechs). The rates of participation in sports were also not significantly different between the groups. The author assesses these results against the ambient levels of air pollution in these two cities, which exceeded desirable levels for sulphur dioxide, nitrogen dioxide and PM_{10} on more days in Prague than in Vancouver. The numbers of days when ozone exceeded desirable levels were similar in both cities. Overall, the author concludes that this study does not support the proposition that increased pollution levels increase the prevalence of asthma by contributing to the development of new disease.

A novel outdoor pollutant postulated to have an influence in causing asthma in urban areas in the USA is methyl tertiary butyl ether (MTBE), an oxidising agent added to gasoline (petrol); (Joseph, 2000). The author points to increases in asthma prevalence in certain cities on the east coast of the USA and relates this to the use of MTBE. The author argues for the necessity of further research to determine the possibility of any link.

A review by Koenig (1999) claims that although there is sufficient evidence for ETS as a risk factor for asthma, and evidence that workplace air pollutants can cause asthma, there is no convincing evidence that common air pollutants are involved in the development of asthma. On the other hand, Sheppard and Kaufmann (2000) argue persuasively for the need for research on the asthma-initiating role of air pollutants. In their view, a prospective birth cohort design would be the most appropriate, with use of cumulative exposure monitoring and subjects exposed to different levels of ambient air pollution.

In a study based in California, USA, the association between playing team sports in different communities with varying levels of atmospheric pollution and the subsequent development of asthma was investigated (McConnell *et al.*, 2002). In this prospective cohort study, a total of 3535 children aged between 9 and 16 years were recruited from schools in 12 communities with differing atmospheric concentrations of ozone, PM_{10} and nitrogen dioxide. Children who had previously been diagnosed as having asthma were excluded. Across all communities there was an increased risk of developing asthma among children who had played three or more team sports in the previous year. In the high ozone communities, children who played three or more team sports had an increased relative risk (RR) for asthma (RR 3.3, 95% CI 1.9–5.8). This increased asthma risk in relation to sports participation was not seen in low ozone communities. There was also a trend of increasing asthma with the number of sports played in the high ozone communities. When the effect of sports was analysed in terms of high and low ozone communities further categorised by high and low levels of

other pollutants, there was no interaction between sports, ozone and other pollutants. The effect of team sports on asthma risk was similar in communities that had high and low levels of PM_{10} and other pollutants. The authors concluded that there was an association between new diagnosis of asthma and heavy exercise in communities with high levels of ambient ozone, and that in these communities the combination of outdoor exercise and air pollution may contribute to the development of asthma in children.

A study centred on three counties in the former East Germany aimed to investigate the prevalence of asthma in these three counties, which had very different outdoor air pollution profiles (Heinrich *et al.*, 1999). The reference county, Zerbst, had no industrial pollution, the main pollution source being domestic heating with brown coal. Another county in the study, Bitterfeld, had ambient air pollution due to emissions from chemical and power plants. The third county, Hettstedt, had air pollution due to dust containing heavy metals from smelters and domestic burning of brown coal. In this cross-sectional study, 2470 children from three school grades between 5 and 14 years of age were selected, with roughly similar numbers from each of the three participating counties. Parents of the selected children completed a questionnaire that, among other questions, asked about whether the child had ever received a physician diagnosis of asthma. The prevalence of asthma was lowest in Zerbst, at 1.6%, with Hettstedt at 2.1% and the highest prevalence being in Bitterfeld at 4.4%. Adjusted ORs with respect to the reference county, Zerbst, were then calculated. Many variables were adjusted for, including birthweight, breastfeeding, parental atopy, housing characteristics, ETS exposure, maternal smoking in pregnancy, contact with pets and daycare attendance. There was no significant difference in the OR for asthma (crude or adjusted) between Hettstedt and Zerbst. However, the adjusted OR for asthma comparing Bitterfeld against Zerbst was 4.40 (95% CI 1.94–10.5). The authors were unable to attribute the difference in asthma prevalence to any specific pollutant; however they mention that the two main air pollutants in Bitterfeld were sulphur dioxide and suspended particulates, while in Hettstedt the main pollutants were lead and cadmium in dust and soil. Interestingly however, with the exception of asthma, other indicators of respiratory ill health (such as wheezing, shortness of breath and cough without cold) had higher ORs for lifetime prevalence in Hettstedt than in Bitterfeld. Also, Hettstedt had significantly higher ORs than Zerbst for one or more positive skin prick test and increased levels of one or more IgE. This phenomenon was not seen in Bitterfeld.

2.2 Indoor environment

In the review by Strachan (2000) of the study of Seventh Day Adventists, a 50% relative increase in asthma incidence was seen over 10 years among lifelong non-smoking adults exposed to ETS compared with those not exposed. Among other conclusions of this review, Strachan (2000) considers that environmental factors are more likely to be related to provocation of asthma attacks than to asthma induction and hence the prevalence of asthma.

With regard to volatile organic compounds (VOCs), a review on indoor pollution and its effect on respiratory health has concluded that there is no evidence for development of new asthma at VOC concentrations at or below 15 mg/m^3 (Bardana, 2001).

A common indoor pollutant reviewed by Delfino (2002) with regard to its relationship between asthma and atopy in children is formaldehyde. One study reported a significantly higher prevalence of asthma (and chronic bronchitis) in children aged 6–15 in households with higher formaldehyde concentrations, defined as over 41 ppb. However, there may have been confounding factors in this study. Also reviewed in this paper is evidence for an association between VOCs and asthma prevalence, but there are insufficient epidemiological data to allow causality to be evaluated for indoor or outdoor VOCs. Delfino (2002) concludes by identifying some areas of research that need to be addressed, and recommends well-designed prospective cohort studies to ascertain the relevance of air pollutants to asthma onset.

In this review Delfino (2002) also addresses adult onset asthma, for which there is some evidence for an association with ETS exposure. A study that followed up 3914 non-smoker adults over 10 years showed a significantly higher relative risk for adult onset asthma after 10 years working with a smoker. Another study of 4197 adults who had never smoked showed a significantly higher OR of developing asthma from any ETS exposure.

In the Taiwanese study discussed above (Wang *et al.*, 1999), ETS *per se* was not statistically significantly associated with asthma (OR 1.02, 95% CI 0.99–1.05 as compared with no ETS). However, when ETS exposure was broken down into two categories, the higher category (≥ 1 pack/day) was significantly associated with increased asthma prevalence (OR 1.13, 95% CI 1.07–1.19). An interesting finding was that use of Chinese incense was associated with a reduced prevalence of asthma (OR 0.88, 95% CI 0.86–0.91). The authors believe this phenomenon to be worthy of future study, despite citing earlier work that stated that Chinese incense contained traces of formaldehyde, a known sensitiser.

The study comparing Norwegian and Russian arctic regions with regard to prevalence of asthma (Dotterud *et al.*, 2000), discussed in Section 2.1, also shed some light on indoor environment factors with regard to asthma. As stated, the prevalences of asthma in two adult cohorts, one located in Norway and the other in Russia, were very similar. The authors pointed out that people in the Russian area were more likely to be exposed to nitrogen dioxide at home, as most homes had a gas stove. Also, the numbers of homes reported to have a damp indoor environment and carpeted floors were higher in the Russian area. Indoor humidity and carpets were seen as risk factors for growth of moulds and mites, and subsequent asthma development. Presence of pets in the home significantly increased the relative risk (RR) for asthma in the Russian region as compared with the Norwegian counterpart. The authors believed that the overall increase in atopic disease (excluding asthma) in the Norwegian area may have been partly due to poor ventilation in the Norwegian homes; however, other factors including consultation behaviours in the two regions may have affected the results.

An extensive review of indoor exposures, by the US Institute of Medicine, looks at a wide variety of different types of exposures in connection with development and exacerbation of asthma[3]. These include biological exposures such as domestic pets, fungi/moulds, dust mites and pollen, and 'chemical' exposures such as nitrogen oxides, particulate matter, sulphur oxides and ETS. The review concludes that there is sufficient evidence of a causal relationship between development of asthma and house dust mite exposure. There is also sufficient evidence for an association between asthma development and ETS in preschool children. There is limited evidence for an association between asthma development and cockroach (in preschool children), and respiratory syncytial virus (RSV). There is inadequate or insufficient evidence to determine whether there is any association between asthma development and various biological factors (for example, cat, dog, domestic birds, rodents, endotoxins, fungi/moulds, houseplants and pollen) and chemical factors (for example, nitrogen oxides, pesticides, plasticizers, VOCs, formaldehyde and ETS in school age and older children and adults).

Another review of indoor exposures and to childhood asthma development points to studies that indicate an association between ETS exposure (particularly maternal smoking) and new incidence of asthma in children under 6 years, but notes that associations between ETS exposure and asthma in older children are less precise (Gold, 2000). In consideration of the role of dust mite in development of asthma, Gold (2000) concludes that there is a strong suggestion that dust mite exposure is a risk factor for the development of symptomatic asthma in children with prior allergy. With regard to cat exposure, there is conflicting evidence for an association with asthma. In a New Zealand study, sensitisation to cat allergen predicted development of asthma in children. However, a Swedish study suggested an inverse relationship between the presence of a cat or dog in the first year of life and both sensitisation to cat and asthma at age 13. There was also some evidence to indicate that bacterial

[3] Institute of Medicine (IOM) (2000) *Clearing the Air: Asthma and Indoor Air Exposures,* Washington DC, USA, National Academy Press, available [March 2003] at http://www.nap.edu/books/0309064961/html/

endotoxin exposure, for example on a farm, may be protective against asthma development. Overall, the author concluded that the data suggested that in already allergic populations, indoor allergen exposure may increase the risk of sensitisation to a specific allergen. Further, indoor allergen exposures may also increase the risk of expression of asthma or persistence of asthmatic symptoms to the point of the individual being labelled asthmatic. As the author points out, the potential roles of allergen exposure in the development of allergy and in localisation of the inflammatory response to the lung are poorly understood.

An Australian study, based in Tasmania, used data from a study conducted in 1988 looking at risk factors related to Sudden Infant Death Syndrome (SIDS) (Ponsonby *et al.*, 2000). This included information regarding the infant's home environment, which could then be linked with data from a 1995 cross-sectional study that obtained information about asthma prevalence. A questionnaire survey was used to obtain the prevalence of asthma in the 1995 cohort, but the question appeared to relate only to 'having asthma', rather than physician diagnosis of asthma. A total of 863 subjects had data from both the 1988 survey and the 1995 survey; in this way, the study can be considered a prospective cohort study. Any links between ETS and development of asthma were somewhat inconsistent, with no clear pattern associating ETS with asthma. Even maternal smoking during pregnancy was not found to be associated with asthma in this study. There was some indication of an association between gas cooking during infancy and asthma, and use of gas heating and asthma, when other potential confounders were adjusted for. Interestingly, in the 1995 analysis, an association was also found between use of hairspray in the baby's bedroom and asthma development. Other indoor environment factors such as cat or dog ownership, presence of mould in the home, and number of people living in the home (six or more), did not appear to be significantly associated with asthma in this study.

An extensive UK based study involving 5687 adults (parents of children included in the National Asthma Campaign Manchester Asthma and Allergy Study), looked at associations between asthma and various exposures associated with the indoor environment (Simpson *et al.*, 2001). In this cross-sectional survey, sensitisation to house dust mite, cat, dog and pollen were all significantly associated with having ever had asthma, as was dog ownership and being a smoker. However, as the authors point out, there is no evidence to indicate that sensitisation to allergens is the cause of asthma.

A large German study looked at the relationship between early exposure to house dust mite and cat allergens and development of asthma in childhood (Lau *et al.*, 2000). This prospective cohort study included participants from five German cities. A total of 1314 newborn babies were selected for the study, of whom 499 were considered to be at high risk for development of asthma by having at least two atopic first degree relatives, or a high cord blood IgE. The children were followed up until the age of seven years. Carpet dust was obtained on three occasions from each child's home until the age of three years, for analysis of dust mite and cat allergens. At age seven years, there were 939 children available for follow up. No consistent relationship was found between doctor-diagnosed asthma and early life exposure to indoor allergens.

A Swedish study (Hesselmar *et al.*, 1999)* found that exposure to pets in the first year of life was associated with lower prevalence of asthma in schoolchildren. An American study, however, found an increased risk for childhood asthma with presence of a dog in the household (Lanphear *et al.*, 2001)*.

A review article looking at the role of ETS in development of asthma among adults included studies that covered ETS exposure in the home and/or workplace (Weiss *et al.*, 1999). In this review the majority (three out of four) studies showed a significant association between adult onset asthma and ETS exposure either at home or in the workplace. The authors conclude that, overall, there are insufficient epidemiological data regarding the role of ETS in asthma causation in adults.

A case–control study based in Plymouth, UK, aimed to investigate any relationship between house moves, heating methods, and asthma in childhood (Jones *et al.*, 1999)*. This study found a non-significant association between early house moves and the subsequent development of asthma. No associations were found between heating methods and asthma (apart from ducted air heating, which

could have arisen by chance owing to small numbers). A US based cross-sectional survey, on the other hand, found a significantly increased risk of asthma in children exposed to a gas stove or oven (Lanphear *et al.*, 2001)*.

The indoor environment within the school was the focus of a study to evaluate the incidence of asthma diagnosis and certain factors in the school environment (Smedje & Norbaeck, 2001)*. In this study, the incidence of asthma diagnosis was higher in pupils of schools with more settled dust and more cat allergen in this dust. Among children with no history of atopy, a new asthma diagnosis was more common at higher concentrations of formaldehyde and total moulds in the classroom air.

A very specific indoor environment, that of the indoor chlorinated swimming pool, has recently been investigated in relation to asthma in Belgian children (Bernard *et al.*, 2003). The aim of this study was to investigate whether exposure to nitrogen trichloride in indoor chlorinated pools affected the respiratory epithelium in children, and hence their risk of developing asthma. A part of this survey included a retrospective analysis of data from an asthma survey conducted in Brussels between 1996 and 1999. The main aim of this survey was to determine the asthma prevalence in a large population of schoolchildren in Brussels. A total of 1881 schoolchildren aged 7–14 years were recruited from 15 schools. Data on respiratory symptoms and lifestyle variables (including socio-economic status, exposure to pets and exposure to ETS) were collected by questionnaire. Asthma was screened for using the exercise-induced bronchoconstriction test, in which a reduction in peak expiratory flow (PEF) by 10% after exercise was taken as a positive result. Total asthma prevalence was calculated as the prevalence of children with a positive PEF test, plus the children who were negative in this test, but who were being treated with medication for asthma (from the questionnaire data). Data on swimming pool attendance by the children were obtained from their schools. All pools had chlorine concentrations within Belgian recommended limits (5–15 mg/l). In this study, total asthma prevalence varied widely between schools, from 5.5% to 30.5%, mean 14.2%. No statistically significant correlation was found between total asthma prevalence and age, sex, the proportion of whites/non-whites, socio-economic status, or the proportion of children exposed to pets or ETS. The only variable to be significantly correlated with asthma was the cumulative pool attendance. Associations between asthma prevalence and pool attendance were strongest when the children were youngest. The associations between asthma prevalence and pool attendance were strengthened when the pool indices were adjusted for pool hall height (as a surrogate for pool air quality), pets and ETS exposure. Other aspects of the relationship between pool attendance and respiratory effects were examined by using outcome measures of serum levels of surfactant-associated proteins to indicate lung epithelial damage (causing hyperpermeability). Similar positive correlations were found. The authors concluded that further research would be useful in determining whether the increasing attendance of chlorinated pools, especially by young children, is relevant to the increasing incidence of asthma in industrialised countries.

2.3 'Hygiene' and related factors

The studies discussed in this section relate to the theory that exposure to allergens early in life confers a protective effect, reducing the risk of asthma later in life. Early exposure to allergens is one consequence of having older siblings; also, as family sizes have declined and more children receive preschool care outside the family residence, early life exposures can come from mixing with other children in various forms of childcare.

A prospective longitudinal study from the USA aimed to clarify the effects on asthma of having older siblings and daycare attendance (Ball *et al.*, 2000). Children were recruited to the study at birth, and were followed up between the ages of 6 and 13 years with four questionnaire surveys to their parents. A child was classified as having asthma if he/she had received a physician diagnosis of asthma and had experienced an exacerbation of their asthma in the previous year. In total, the parents of 1035 children completed at least one follow-up questionnaire and were included in the analysis. In this survey, increasing numbers of older siblings was associated with a decreased risk of asthma. With the

RR of asthma in a child with no older siblings set to 1, the RRs for having one, two, and three or more older siblings were 0.9 (95% CI 0.7–1.0), 0.7 (95% CI 0.5–1.0) and 0.6 (95% CI 0.4–1.0) respectively. The authors quote a p value of 0.03 for trend. Entry into daycare at age 0–6 months was also associated with a decreased risk of asthma compared with entry at older than 12 months (RR 0.4, 95% CI 0.2–1.0). Entry into daycare at 7–12 months was not significantly associated with reduced asthma risk.

One recent study serves to clarify the effect of childcare on the development of asthma, with evidence restricting the effect to certain children only. An original cohort of 453 children with a parental history of atopy was followed up until 6 years of age. A significantly reduced incidence of asthma and recurrent wheeze at age 6 was found among children with no maternal history of asthma who had attended day care in the first year of life, compared with those who had not (Celedón *et al.*, 2003). However, for children who did have a maternal history of asthma, such a protective trend was not seen.

The review by Nolte *et al.* (2001), citing from other work, mentions the debate regarding whether multiple viral infections may have an effect on the development of asthma, an alternative explanation being that some children are more susceptible to asthma and are thus more likely also to suffer from respiratory tract infections. Also mentioned is the theory that foodborne infections associated with (poor) hygiene appear to confer a protective effect against asthma development.

Abramson and Walters (2000)* argue that childhood infections are a part of normal maturation of the immune system and asthma is a manifestation of a persistent 'immature' immune system. A study possibly linked with the hygiene hypothesis is that by Hesselmar *et al.* (1999)*, discussed in Section 2.2, which found that exposure to pets in the first year of life was associated with lower prevalence of asthma in schoolchildren.

2.4 Maternal and birth factors

Maternal and birth factors are those affecting the fetus *in utero*, and factors coming into play at and around parturition, such as occurrence of an instrumental delivery or Caesarean section.

Maternal smoking is one of the major prenatal influences on asthma as discussed in a review of pre-, peri- and postnatal factors in asthma development (Brown & Halonen, 1999), in which the work of many authors is cited. Maternal smoking during pregnancy has been found to increase cord IgE and IgD, thus increasing the risk that the newborn will develop atopic disease before 18 months. The difficulty of separating *in utero* maternal smoke exposure and postnatal ETS exposure was acknowledged [although the Gilliland *et al.* (2001) study described below has addressed this issue). No available studies had demonstrated any association between *paternal* smoking (prenatally or postnatally) and childhood asthma. The role of *in utero* sensitisation to allergens and the potential to bias the fetus towards a T-cell Th2 phenotype is also mentioned, as are placental factors that may influence fetal immune development. When discussing peripartum influences on asthma, obstetric practices such as use of prostaglandins and hormones are mentioned, alongside the natural presence during parturition of various hormones, prostaglandins and cytokines. Further investigation into the role of perinatal factors in asthma, both natural and iatrogenic, is warranted. Although obstetric factors such as pre-term birth, low birth weight independent of gestational age and young maternal age have been associated with increased risk of wheeze or asthma in childhood, the authors believe that these are more likely to be indicative of other social or biological factors that are responsible for the true increased risk of asthma.

Looking at postnatal events, Brown and Halonen (1999) considered the role of infection in modulating asthma. Infection has been seen as both having a potential causative role in asthma, and, more recently, being a protective factor, mitigating against asthma development. Although viral infections often cause acute wheezing and other respiratory symptoms, any role they may have in the

pathogenesis of asthma is not clear. It may be that infections in early life play a role in biasing the immune system towards a Th2 cell predominance. This type of immune profile would tend the individual towards asthma and atopic diseases. Bacterial infections would steer the individual towards a Th2 cell predominance and viral infections away from such a predominance. Further data in this field from prospective longitudinal studies would be of benefit in clarifying this issue. The influence of breastfeeding on asthma and other atopic diseases was also covered in this review. A putative effect of breastfeeding in modulating immune function in the infant was described but no studies relating breastfeeding history to asthma development in later life were presented. In conclusion, these authors thought it likely that asthma development in any one individual was a result of an interplay between genetic predisposition and environmental factors that modulated the genetic base to result in the phenotype of disease experienced by the individual.

A study in Finland has investigated the association between type of delivery and asthma at age 7 (Xu *et al.*, 2000). This study involved a prospective birth cohort of 8088 children. Data collection took place during pregnancy and at age 7. The presence of asthma in each subject was ascertained by a questionnaire, completed by the parents, enquiring about long-term illnesses including asthma. It appears that parents were simply asked whether their child suffered from asthma, rather than whether they had received a diagnosis of asthma from a physician, which could lead to inaccurate results. This study found an increase in asthma prevalence among children who had received clinical interventions during delivery. Three categories of intervention were investigated; Caesarian section, vacuum extraction and 'others' (including forceps, manual extraction and extraction breech). In comparison with children delivered normally, the OR for Caesarian births was 1.38, with a 95% CI of 1.00–1.92, indicating borderline significance. For vacuum extraction, the OR was 1.32, with a 95% CI of 0.80–2.19, while in the 'others' category the OR was 2.19 with a 95% CI of 1.06–4.33. The 'others' category was, however, the smallest, with 131 in total in this category and only nine cases of asthma. Potential confounders such as sex, birth weight, gestational age and maternal allergies were taken into account. As part of the same study, the association between Apgar[4] score at the 1st, 5th and 10th minutes and asthma at age 7 was also investigated. Asthma appeared to be more prevalent among children with lower Apgar scores (divided into three categories, 9–10, 7–8 and 0–6). However, there were smaller numbers in total in the groups with lower Apgar scores and smaller numbers of asthma cases. On analysis of the ORs, the only group with a significantly higher OR for asthma was the group with an Apgar score of 7–8 at 1 minute (OR 1.36, 95% CI 1.02–1.83). The same set of potential confounders as for delivery method was also taken in to consideration. Overall, this study provides some indication of an association between delivery methods and condition at birth and asthma in childhood, but the evidence is not strong. As mentioned above, the method of ascertaining asthma leaves room for error as it was not based on physician diagnosis but on parental response to a questionnaire. Also, there were only small numbers of asthma cases in some categories.

A large cross-sectional survey in Southern California used a self-administered questionnaire to investigate the effects of *in utero* exposure to maternal smoking, and of present and previous ETS exposure (Gilliland *et al.*, 2001). In total, 5762 children from public schools participated in the project. The majority of students were 10 years or younger, white and from households with health insurance and high educational attainment. Only 1.7% of children were active smokers themselves, while 18.8% had been exposed *in utero* to maternal smoking and 16.0% had experienced both *in utero* smoking and ETS. A total of 161 women had smoked during pregnancy, but then reported no ETS exposure to the child within the home after birth. In this study, among all subjects, *in utero* exposure to maternal tobacco smoke, without exposure to ETS, was significantly associated with physician-diagnosed asthma and wheezing (OR 1.8, 95% CI 1.1–2.9). Postnatal ETS exposure, without prior exposure to maternal smoking *in utero,* was not associated with asthma. Exposure to maternal smoking *in utero*, followed by exposure to ETS, did not further increase the OR above that for *in utero* exposure alone (OR 1.3, 95% CI 1.0–1.7). Closer analysis of the results however, showed that

[4] The Apgar score is a score out of 10, based on the condition of the newborn, determined at 1 minute after birth and then at 5 minutes and possibly at further intervals after birth if required. The Apgar score indicates when resuscitation measures are necessary. A score of 7–10 is considered normal

only in subjects ***without*** a family history of asthma did the association between *in utero* maternal smoking and asthma achieve borderline significance (OR 1.9, 95% CI 1.0–3.7). The corresponding OR for *in utero* maternal smoking and ETS exposure within this group was 1.4, 95% CI 1.0–1.9. In children ***with*** a family history of asthma, no significant increased risk for development of asthma with maternal smoking *in utero* or ETS exposure was found. Family history of atopy did not seem to modify the influence of maternal smoking *in utero* or ETS exposure, as there were no significant correlations between these factors and asthma in children with or without atopy in their family. In this study, household income was not strongly associated with asthma, but asthma was more common in children born preterm and in African Americans, and less common in children with a parent who had less than high school education. Despite the many limitations of this study, such as the cross-sectional design and various sources of bias and confounding, it provides some evidence to support a link between maternal smoking during pregnancy and subsequent asthma in the child, independent of postnatal ETS exposure. Such a link is possibly restricted to those children with no family history of asthma; however, an influence among children from families with a history of asthma cannot be ruled out.

In a review of factors relating to air toxicants and asthma onset (see Sections 2.1 and 2.2), Delfino (2002) refers to several other studies that also point to maternal smoking during pregnancy being of greater significance in asthma onset than ETS exposure later in life.

An extensive study from Finland looked at the role of perinatal factors in the development of asthma at age 16 (Räsänen *et al.*, 2000). In total, 3065 sets of twins born in 1975–1979 were included in this cross-sectional survey. The outcome variable was the presence of physician-diagnosed asthma, as ascertained from a questionnaire to the parents. Among the results of this study, comparing asthmatic and non-asthmatic subjects, was the observation that asthmatics had a slightly higher mean ponderal index[5] ($p < 0.05$) than non-asthmatics (25.8 as opposed to 25.2). When comparing ponderal index in the lowest quartile with ponderal index in the highest quarter with regard to asthma risk, the OR ratio in the lowest quartile for ponderal index was set at 1 (with adjustment for zygosity, birth order, sex, number of older siblings, parental asthma and maternal smoking). The highest quartile group had an OR of 1.86 (95% CI 1.13–3.07). Another factor found to be significantly different in subjects with and without asthma was mean maternal age at birth. However, the mean ages in both groups were within 12 months of each other; the mean maternal age in non-asthmatics was 28.3 years, compared with 27.5 years in asthmatics. In a model where adjustment was included for the previously mentioned factors, maternal age (<25) did not significantly increase asthma risk. Mean values for birth weight, gestational age and Apgar score did not differ significantly between the asthmatic and non-asthmatic groups. On combining several perinatal risk factors into a single model, ponderal index, maternal smoking, parental asthma and number of older siblings (2 or more older siblings being associated with lower asthma risk) all had an independent effect on asthma risk. In this model, other factors such as neonatal hospitalisation, maternal age, sex and parental hay fever did not appear to be independent risk factors for asthma.

In a cross-sectional study, Litonjua *et al.* (1998) examined the relative contributions of maternal and paternal asthma, eczema and hay fever on the risk of asthma and other allergic conditions in their children. The sample comprised 306 siblings of index case children in 217 families, where one or both parents had a medical diagnosis of asthma, hay fever, eczema or allergies. Maternal history of asthma was found to be more strongly associated with asthma than paternal history. Among children under 5, the OR of asthma when maternal asthma was present was 5.0 (95% CI 1.7–14.9), while in this age group the OR when paternal asthma was present was 1.6 (95% CI 0.5–5.9). For children aged 5 and over, the OR of asthma when maternal asthma was present was 4.6 (95% CI 1.1–19.0), while the equivalent statistic regarding paternal asthma was an OR of 4.1 (95% CI 1.0–16.0). These results were unchanged when controlled for other maternal and paternal conditions. Overall, it was seen that the risk of asthma in childhood was increased by the presence of asthma in the parents, and the results

[5] Ponderal index is a measure of fatness or thinness, often used as an index of nutritional status at birth. Calculated as birth weight (kg)/cube of birth length (m^3) (Räsänen *et al.*, 2000)

suggested that maternal asthma had a stronger influence than paternal asthma, especially in children under 5. Risk of childhood asthma also increased with an increase in the number of parents with the condition. The authors speculated as to whether the increased influence of maternal asthma on childhood asthma was related to genetic factors, placental transfer of maternal factors, and/or to environmental factors, and concluded that further research was needed.

A large British cohort study of 4065 children of 2583 mothers investigated whether *in utero* and perinatal influences contributed to the development of asthma (Annesi *et al.*, 2001)*. In this study, childhood asthma was more frequently reported when there had been health complications during pregnancy, labour or delivery. Specific causes of health complications during pregnancy that significantly related to asthma development were early or threatened labour, and fetal malposition or malpresentation.

Similarly, a Norwegian study found increased risk of asthma in childhood in cases where there had been uterus-related complications (antepartum haemorrhage, preterm contractions, placental insufficiency and restricted growth of the uterus) during pregnancy (Nafstad *et al.*, 2000)*. However, other pregnancy complications such as hyperemesis, hypertension and pre-eclampsia, did not show an association with childhood asthma.

In a review paper, Beasley *et al.* (1999)* consider epidemiological studies investigating the relationship between enhanced fetal growth and an increased risk of asthma and/or atopy. Some, but not all, of these studies report an association between enhanced fetal growth and asthma and/or atopy. The authors hypothesised that factors responsible for fetal growth may also lead to programming of the respiratory or immune systems with a predisposition for development of asthma and/or atopy. The increasing prevalence of these conditions may be related to improved antenatal health in recent decades, as measured by anthropometric measurements at birth.

However, other studies have indicated an association between low birth weight and asthma. An American study (Brooks *et al.*, 2001)* demonstrated independent associations between asthma and very low birth weight (<1500 g at birth) and moderately low birth weight (1500–2499 g at birth). In a British study, the prevalence of asthma at age 26 fell with increasing birth weight (Shaheen *et al.*, 1999)*.

A UK based study examined the relationship between head circumference and other anthropometric measurements at birth and asthma (Gregory *et al.*, 1999)*. Perinatal variables investigated included birth weight, circumference and gestational age in a sample of 239 subjects aged 6–23 years. There was, however, no consistent association between head circumference (or any of the other perinatal variables) and clinical asthma.

A longitudinal study from New Zealand followed up 734 subjects to investigate a relationship between reported asthma at age 13 and anthropometric measurements at birth (Leadbitter *et al.*, 1999)*. Recent asthma symptoms were positively associated with length at birth but not with head circumference.

Maternal infections during pregnancy was found to be significantly associated with childhood asthma in a British case–control study (Hughes *et al.*, 1999)*. This association was found to be slightly stronger in cases of maternal infection during the first trimester and for mothers with cough during pregnancy. There was also an association with number of presentations for respiratory infections (during pregnancy) and childhood asthma (in the offspring). Other independent variables including gender, maternal smoking, maternal wheeze, allergic rhinitis, eczema, asthma treatment in pregnancy and deprivation were allowed for in the analysis, but the associations mentioned remained significant.

This correlation between maternal infections during pregnancy and asthma was also found in a study by Xu *et al*. (1999)*. This Finnish study investigated 8088 children, using asthma prevalence at age 7 as the outcome variable. Children had a higher risk of asthma if their mother had experienced

vaginitis or febrile infections during pregnancy. Maternal febrile infections appeared to be correlated with asthma risk in the offspring according to the timing during gestation of the infection. Infection during the first trimester carried the highest risk of asthma in the child, followed by infection in the second and then third trimesters.

2.5 Drug-related factors and immunisation

In a study to investigate the incidence of asthma in relation to antibiotic use in the first year of life, 505 infants with a history of asthma or allergy in at least one parent were recruited into a prospective cohort study (Celedón *et al.*, 2002). Data were gathered on the administration of antibiotics to the infant during the first year of life, and on the presence of wheezing from 2 to 5 years of age. No significant association was found between use of antibiotics in the first year of life and persistent wheezing, or asthma at 5 years of age. However, maternal history of asthma (see also Section 2.4 above) and male sex were associated significantly with persistent wheezing. After excluding children who were given antibiotics in response to a condition associated with wheeze, no association was found between antibiotic use and transient wheeze. Hence, this study does not support the results of earlier retrospective studies claiming an association between use of antibiotics in early life and risk of asthma.

The association between early antibiotic use and asthma was investigated by Wjst *et al.* (2001)*. This study, based in the former East Germany, found that asthma diagnosis was associated with increasing numbers of courses of antibiotics. However, this association could be due to the treatment of early respiratory infections (an early symptom of asthma) with antibiotics, rather than demonstrating a causative role for antibiotics.

A BMJ report discusses the results of the European Community Respiratory Health Survey, a cross-sectional survey involving 22 countries mostly within Europe (Dyer, 2001). A connection between asthma and paracetamol use was proposed based on the results of this survey, with asthma being more prevalent in those countries with higher paracetamol sales per person. These countries were largely also English-speaking countries; once the 'anglophone effect' was controlled for, it was found that much of the association between asthma and paracetamol disappeared. However, this has been proposed as an area worthy of specifically designed research to investigate further. The apparent association between paracetamol and asthma in adults and children is mentioned in another report of the same study (Janson *et al.*, 2003).

A case–control study of children aged 7–9 years in New Zealand found no significant association between asthma and having vaccinations for polio, hepatitis B or measles/mumps/rubella (Wickens *et al.*, 2001)*. However, the authors cautioned that the role of vaccinations in development of asthma required further research.

2.6 Dietary factors (including breastfeeding)

A potential link between dietary salt intake and risk of asthma is discussed in a review by Seaton *et al*. (2000). On reviewing several studies, the authors conclude that salt intake may have a weak effect on bronchial hyper-reactivity, but in terms of a link between salt and allergic disease, it is more likely that salt intake is a marker for an overall poor diet, rather than being responsible for increased allergic disease. The authors point to a Canadian study that demonstrated no association between dietary salt intake and asthma.

A further dietary feature hypothesised to impact on asthma risk is intake of antioxidant vitamins. A prospective study of nurses in 1995 by Troisi *et al*., (cited in Seaton *et al.* (2000)), showed a reduced risk of onset of asthma among those with the highest Vitamin E intake. Seaton *et al*. (2000) suggested that, for adult onset asthma, there is some association with low intake of vitamins C and E. A Saudi

Arabian study reviewed by Seaton *et al*. (2000) showed increased risk of asthma to be associated with diets low in vegetables, milk, fibre, vitamin E and calcium.

There has also been some research on the subject of asthma in association with dietary fats. In a long-term Swedish cohort study of males born in 1914 (as cited in Seaton *et al.* (2000)), the lifetime risk of physician-diagnosed asthma was significantly greater in those with a high fat intake. Citing the work of other authors, Seaton *et al.* (2000) discuss the hypothesis that the increase in allergic disease may be related to reductions in intake of ω-3 fatty acids (such as linolenic acid) and increased intake of ω-6 fatty acids (such as linoleic acid), and mention a study in which high consumption of oily fish was associated with a reduced risk of asthma in children.

Citing the work of other authors, a review by Nolte *et al.* (2001) discusses an increase in asthma prevalence among Inuit Greenlanders that was seen when they moved to a modern industrialised country and adopted a Western lifestyle with less fish in the diet.

An association between introduction of cereals in the diet of children and risk of grass pollen asthma has been found (Armentia *et al.*, 2001)*.

Breastfeeding in relation to onset of atopic disease is a major topic of discussion. The evidence for breastfeeding reducing the risk of asthma and atopic disease in general is reviewed by Seaton *et al.* (2000). These authors cite many original studies, although it should be pointed out that many studies relate to atopic diseases in general, or other atopic diseases than asthma, such as eczema. Other studies use illness outcomes such as 'wheezing illness' rather than asthma *per se*. In their conclusion, Seaton and colleagues claim that the effects of breastfeeding on atopic disease remain uncertain. Although studies in the past 10 years have increased the evidence for a protective effect of breastfeeding against asthma development, negative studies are still being reported.

An Australian survey of prevalence and risk factors for asthma in preschool children (Haby *et al.*, 2001)* found that breastfeeding significantly reduced the risk of asthma, while a high dietary intake of polyunsaturated fats significantly increased asthma risk.

Another Australian study (Oddy, 2000)*, which took the form of a prospective cohort study, found that the introduction of milk other than breast milk before the age of 4 months was associated with increased risk of asthma at age 6 years. Hence, there was a substantial reduction in risk of asthma at age 6 years in children who received exclusive breastfeeding until at least 4 months of age.

A Japanese study, however, has found contradictory results in relation to breastfeeding and asthma development (Takemura *et al.*, 2001)*. This large study looked at the prevalence of asthma in children who had been breastfed in comparison with those who had received artificial feeding. In this study, a significantly higher prevalence of asthma was found among those who had been breastfed.

The relationship between breastfeeding and childhood asthma was investigated with regard to the potential modifying effect of maternal asthma (Wright *et al.*, 2001)* (see also Section 2.4). This study found that atopic children with asthmatic mothers had increased risk of asthma at age 6 years if they had been exclusively breastfed. This relationship was not seen among children who did not fulfil both criteria of having an asthmatic mother and being atopic themselves.

2.7 Body factors

The question of a possible connection between obesity and asthma has engaged interest over recent years, due to increased prevalences of both conditions. Although any connection between these conditions could take a variety of forms (or possibly many forms with different ones existing in different individuals) an investigation of the correlation between these conditions is nevertheless of interest and relevance.

A Canadian survey, involving 17 605 subjects (9557 females) investigated effects on asthma of smoking and obesity (Chen *et al.*, 1999). All subjects were aged 12 or over. Individuals were considered asthmatic if they had been diagnosed as such by a health professional. In female subjects in two age groups (<25 and ≥25 years) there was a significant increased OR for asthma in association with a body mass index[6] (BMI) of 25 kg/m^{2}and over. This association was not seen in male subjects. Moreover, there was a linear association between prevalence of asthma in females and relative body weight. The authors put forward several potential relationships between asthma and obesity. Obesity may be a causative factor in asthma, with postulated mechanisms involving a reduction of progesterone levels in obese females, causing downregulation of adrenoreceptors and disrupting asthma control. This could account for an association between obesity and asthma being seen in females but not in males. Alternatively, obesity may put the individual at greater risk of developing respiratory symptoms similar to asthma by some physiological mechanism (hence leading to increased diagnosis of asthma among obese people, including misdiagnosis if asthma is not the underlying cause of the symptoms). A further possibility is that asthma and obesity may both result from a common risk factor such as poor diet. Another potential common risk factor may be a sedentary lifestyle with much time spent indoors, which may predispose to both obesity and exposure to possible asthma risk factors such as indoor air pollutants. There may also be common genetic risk factors for both asthma and obesity. An asthmatic individual may be at greater risk of developing obesity if their exercise tolerance and inclination towards exercise are reduced by their condition. As the authors commented, the only one of these theories that supports the observed gender difference in the association between asthma and obesity is the mechanism relating to obesity and female sex hormones.

A British study used a large cross-sectional analysis of English and Scottish primary school children aged 4–11 years to investigate whether there was any consistent association between fatness and asthma symptoms (Figueroa-Munoz *et al.*, 2001)*. The children were categorised as belonging to an English or Scottish 'representative' sample or to an English inner city sample. BMI was used as a measure of fatness. Information collected regarding a child's asthma status included attacks in the previous year, occasional wheeze or persistent wheeze. In this study, BMI and asthma (asthma attacks or wheeze) were found to be associated in a 'representative sample' of children (in girls and boys). In the inner city sample, there was a stronger association of BMI and asthma in girls than in boys, but this effect was less convincing in the 'representative sample'. The authors concluded that obesity was associated with asthma regardless of ethnicity, and with some evidence to indicate that the association is stronger in girls than in boys, but only in a multiethnic inner city sample.

However, another British study (Chinn & Rona, 2001)* found no changes in ORs for asthma before and after adjustment for BMI for both girls and boys. The authors state that the lack of effect of adjustment for BMI was due to a change in association between BMI and symptoms over time. It was concluded that trends in increased body weight do not explain the increase in asthma. Obesity may be a marker of recent lifestyle differences now associated with both asthma and obesity.

An Australian study (Schachter *et al.*, 2001)* found that subjects with severe obesity reported more wheeze and shortness of breath, which may be suggestive of a diagnosis of asthma. However, levels of atopy, airway hyperresponsiveness and airway obstruction did not support the suggestion of a higher prevalence of asthma among this group.

Taking as a context previous associations found between obesity and asthma in female adolescents and adults, a questionnaire survey was conducted with the aim of discovering whether there is a similar sex-specific association in young children (Von Kries *et al.*, 2001)*. Questionnaire data were gathered from 9357 German children aged 5 or 6 years from rural areas, including data on asthma, hay fever and eczema. In this study, 'overweight' was defined as a BMI greater than the 90th centile or equal to the 97th centile, and obesity was defined as a BMI greater than the 97th centile. The adjusted OR for asthma in girls was 2.12 (95% CI 1.22–3.68) for the overweight group, and 2.33

[6] BMI = weight (kg)/height (m)^2

(95% CI 1.13–4.82) for the obese group. No relation between weight and asthma was seen in boys. Other atopic conditions such as hay fever and eczema were unrelated to weight in both sexes. Hence, the authors hypothesised that the sex-specific association between asthma and weight discovered in females was not related to a mechanism of atopic sensitisation.

An American study found that the prevalence of asthma rose significantly with increasing quartiles of BMI (Von Mutius *et al.*, 2001)*. After adjustment for confounders a significant positive association remained between BMI and asthma. No independent relationship between BMI and atopy was found. In this study, no effect modification by sex or ethnic group was found.

Another body related issue in the development of asthma is that of physical fitness. It is known that physical exercise may induce symptoms of asthma, and there is a question that physical fitness may also be protective against asthma. A prospective study aimed to address the issue of whether physical fitness in childhood impacted on development of asthma (Rasmussen *et al.*, 2000)*. Physical fitness was found to be inversely related to the development of asthma diagnosed by a doctor.

2.8 Miscellaneous factors

There has been some suggestion that living in a farm environment in early life may have a protective effect against the development of asthma. In an editorial review, Braun-Fahrländer (2001) mentions the work done by research teams covering Austria, Switzerland and southern Germany. In this study, the risk of asthma was reduced among children who had had contact with stables in the first year of life, compared with children with no such exposure, or exposure later in life. There was also an independently associated risk reduction for asthma in children who had consumed farm milk in the first year of life. Braun-Farhländer (2001) cites a Nepalese study in which keeping cattle inside the family home was associated with a reduced asthma risk, while keeping cattle outside the home was not. He also cites a study from Finland, in which students aged 18–24 who were raised on farms during the first 5 years of life had a reduced risk for physician diagnosed asthma, whereas students from a rural non-farm environment had a comparable risk to that of students who had had urban childhoods.

The review by Nolte *et al.* (2001) discusses work of other authors that compares the prevalence of asthma in Inuit Greenlanders living in a rural or urban setting in Greenland or Denmark. Asthma prevalence was higher among Inuits living in urban environments, indicating that lifestyle factors related to urban living had an important influence. This review also cites previous studies showing a reduction in asthma associated with childhood contact with livestock and poultry, and the possible protective effect of endotoxins to be found in farm environments.

While the primary focus of a Finnish study was the investigation of cancer incidence in residents of housing built on the site of a rubbish dump (Pukkala & Pönkä, 2001), this study also included a comparison of asthma incidence. The landfill site had taken both household and industrial waste, and there had been an incident of a depression occurring in the soil in the yard of one of the residences. On investigation, waste was revealed that was subsequently identified as containing cyanides. Hence, there was concern about the health of the residents regarding possible exposure to toxins. In the dump area cohort, 957 men and 1057 women were included in a comparison for cancer incidence; it is assumed that similar numbers were used in the asthma study. A comparison of asthma incidence between residents of the housing built on the site of the dump and occupants of reference housing (housing of similar type but not located on the landfill site), was performed. For both groups, standardised incidence ratios (SIRs) were obtained using age and sex specific incidence rates for Helsinki as a whole. The dump area cohort had a significantly higher asthma incidence than for Helsinki overall, while the referent housing cohort did not. In a comparison between the dump area cohort and the referent housing cohort, the incidence of asthma in the dump cohort was significantly higher. As a part of this study, concentrations for several different toxins, such as metals, cyanides, VOCs, and PAHs, were determined in soil samples. Although it would not be possible from this study

to attribute the increased asthma incidence to any one factor, the authors considered it possible that part of the increased asthma incidence may have been due to exposure to dump toxins.

3 Discussion and analysis[7]

One of the main findings to come out of this project has been the wide-ranging literature available on the non-genetic causal factors behind the development of asthma.

Other researchers have conducted comprehensive searches on multiple bibliographic databases with the specific aim of evaluating the scientific literature on exposure to airborne toxic chemicals and the development and exacerbation of asthma in the general population (Barry *et al.*, 2002). The strategy used by Barry *et al.* (2002) involved searching 11 bibliographic databases, including MEDLINE® and EMBASE®. The searches looked for papers discussing links between asthma and 188 hazardous air pollutants, and incorporated additional specific search terms such as volatile organic compounds (VOCs), plasticizers, metals and environmental tobacco smoke (ETS). These searches yielded over 5000 references. Although some of these papers may have looked only at exacerbation of asthma and not at development, the large number of papers is indicative of the size of the knowledge base in the area of asthma and toxic airborne chemicals, which is only one potential element of environmental influences on the development of asthma.

The sheer diversity of the different causal factors hypothesised, from environmental factors such as home environment, indoor pollutants and external air pollution, to more individual factors such as body size or birth factors, is very apparent. The widely observed increase in incidence of asthma may have not one underlying cause but several, possibly interacting with each other, with different factors playing a greater or lesser role in different geographical areas. The geographical locations between which differences in asthma incidence and underlying causal factors occur may not be very distant from each other, but could vary according to an urban/rural environment, or due to differences in housing type or other factors.

Outdoor air pollution has been one of the main areas of interest in this report. Some of the evidence examined has pointed to a role for outdoor air pollution in asthma development. For example, the review by Stone (2000) pointed to a Dutch study in which asthma was more frequent in children close to a freeway than in other children. Other evidence for a link between traffic exposure and asthma comes from a review by Delfino (2002), who reports on several studies indicating an association between asthma prevalence and traffic exposure. Pollutants associated with asthma (from various studies reviewed) include carbon monoxide, nitrogen oxides, polycyclic aromatic hydrocarbons (PAHs), sulphur dioxide, benzene and methyl tertiary butyl ether. When considering the nature of traffic pollution, it is important to be aware that the pollutants selected by the researchers for analysis may not themselves be directly related to asthma, but may be acting as markers for other pollutants that are directly associated with asthma. Hence, further research in this area is necessary to develop knowledge of those specific pollutants that may be associated with asthma, or indeed whether it is the mixture of pollutants produced by motorised vehicular transport that may have a causal link with asthma.

Other exposures associated with outdoor air pollution have been associated with asthma development. Strachan (2000) reviewed a study from California in which onset of asthma in adulthood was linked with outdoor exposure to particulate air pollution. The same cohort of subjects, reviewed by Delfino (2002) revealed associations between asthma and outdoor concentrations of total suspended particulates, total suspended sulphates and, in males only, ozone.

The study by McConnell *et al.* (2002), based in California is especially interesting, as it attempts to address the interaction between outdoor exercise and ozone levels in the development of asthma in children. Those children in the high ozone areas who also had high participation in sports were found to have an increased risk of asthma; this increased risk with sports participation was not seen in the

[7] For references marked with an asterisk, only the abstract was reviewed

low ozone communities. Furthermore, when potential effects of other pollutants were considered, there was no interaction between sports, ozone levels and levels of other pollutants.

In a more general way, studies that have investigated the prevalence of asthma in relation to urbanisation, such as the study by Lin *et al.* (2001), which found increased asthma prevalence in more highly urbanised areas in Taiwan, also lend weight to the theory of outdoor air pollution being connected with asthma prevalence. In addition, this study (Lin *et al.*, 2001) found a correlation between carbon monoxide level and risk of asthma. The review by Delfino (2002) provides overall support for the view that asthma and atopy are more frequent among people living near heavy traffic.

Another study of great interest is that of Heinrich *et al*. (1999), who investigated prevalence of asthma in children in three regions of the former East Germany. There was a higher risk of asthma among children in a county where air pollution comprised mainly sulphur dioxide and suspended particulates, as compared with a reference county with no industrial pollution. A county in which the main pollutants were lead and cadmium in dust and soil did not show increased asthma risk in relation to the reference county.

Other researchers in the field of asthma, however, have not supported the view that outdoor air pollution is associated with asthma. For example, a review by Peden (2000) concludes that there is no clear indication that ozone, sulphur dioxide or nitrogen dioxide have any role in asthma pathogenesis. An interesting study investigating asthma prevalence in two arctic regions, one in Russia, one in Norway, found no significant differences in asthma prevalence in adults between the two regions (Dotterud *et al.*, 2000). In the Russian area, outdoor air pollution was higher, including sulphur dioxide, particulates and heavy metals. However, neither area had high levels of traffic or nitrogen dioxide. Similarly, a study comparing asthma prevalence among teenagers in Vancouver, Canada, and Prague, Czech Republic found no significant differences between the two cities (Vacek, 1999). This was despite higher levels of sulphur dioxide, nitrogen dioxide and particulate matter of mean aerodynamic diameter less than 10 μm (PM_{10}) in Prague than Vancouver, although ozone levels were similar in both cities.

Given the disparity of results between different studies investigating the role of outdoor air pollutants, it is difficult to form any overall conclusion as to their potential role in asthma induction in some individuals. A more systematic and thorough analysis of available evidence is required to make a balanced judgement. This may highlight the need for further research in this area, to identify particular pollutants or sources of pollutant mixtures that may be at least partially responsible for asthma prevalence in industrialised and urbanised areas.

As well as the concerns regarding outdoor air pollution, the indoor environment has also come under scrutiny as a possible source or location of environmental factors that may have a causal role in asthma.

One factor of particular interest is environmental tobacco smoke (ETS). There is a body of data on this topic; for example Strachan (2000) reviews the California-based studies of Seventh Day Adventists, which found an increase in asthma incidence in non-smoking adults exposed to ETS. Delfino's review (2002) also reports studies that have shown increased risk of asthma among adults exposed to ETS. However, reviewing the influence of ETS exposure in both the home and workplace, Weiss *et al*. (1999) conclude that there are insufficient epidemiological data to allow an overall conclusion to be made with regard to ETS exposure and asthma causation in adults. This is despite their finding that three out of four studies reviewed indicated a significant association between adult onset asthma and ETS exposure in the home or workplace.

The Taiwanese study of Wang *et al.* (1999) discovered an association between ETS and asthma in children aged 11–16 years only at higher levels of ETS exposure. In a review of indoor exposures and asthma in childhood, Gold (2000) includes studies that indicate a link between ETS (especially due to maternal smoking) and asthma incidence in children under 6 years, but concludes that ETS exposure

and asthma in older children are less precisely associated. An Australian study found no clear pattern of ETS exposure in relation to asthma development in children (Ponsonby *et al.*, 2000). Overall, there appears to be some evidence for an association between ETS and asthma in children. The ages at which children are susceptible to such exposure, and the degree of exposure that poses a risk, are less certain, and may indeed vary from child to child.

Another aspect of the indoor environment that has caused concern with regard to asthma causation is the method of heating and/or cooking used in the home. The Australian study (Ponsonby *et al.*, 2000) found some indication of an association between asthma and gas cooking during infancy, also between asthma and gas heating. A US-based cross-sectional survey also found an increased risk of asthma in children exposed to a gas stove or oven (Lanphear *et al.*, 2001)*. Conversely, no association was found between heating methods and asthma in a UK-based case–control study (Jones *et al.*, 1999)*.

Indoor pollutants investigated in relation to asthma causation include VOCs. The general conclusion from the evidence discussed in this review is that there is insufficient evidence to indicate an association between VOCs and asthma. Delfino (2002) reviews a study with a significantly higher asthma prevalence in children from households with higher formaldehyde concentrations, and another study reports that new diagnosis of asthma was more common with higher levels of formaldehyde (and total moulds) in classroom air (Smedje & Norbaeck, 2001)*. However, a US review of indoor exposures with regard to asthma development and exacerbation[8] concluded that there was insufficient or inadequate evidence to allow any conclusions to be drawn on whether there is any association between asthma development and volatile organic compounds (VOCs) or formaldehyde.

The presence of allergens within the indoor environment is another contentious issue with regard to asthma causation. Such sources of allergens may include dust mites, pets, or moulds. The US review of indoor exposures[1] concluded that there is sufficient evidence of a causal relationship between asthma and house dust mite exposure, as well as limited evidence for such an association between asthma and cockroach in preschool children. However, there was thought to be inadequate or insufficient evidence for such an association between asthma and other sources of allergens including cat, dog, domestic birds, rodents, endotoxins and pollen.

Hence, the role of allergens in the causation of asthma among individuals who do not have a pre-existing disposition to allergy and/or asthma is obscure. For example, the study by Lau *et al.* (2000) found no consistent relationship between asthma and early life exposure to dust mite and cat allergens. On the other hand the study of Smedje and Norbaeck (2001) found increased incidence of asthma diagnosis in pupils of schools with more settled dust and cat allergen in the dust, and also if there were higher concentrations of moulds in the classroom air.

In Gold's review (2000) of the evidence surrounding allergen exposure and asthma, it is concluded that in already allergic populations, exposure to indoor allergens may increase the risk of sensitisation to a particular allergen and may also increase the risk of expression of asthma or persistence of asthmatic symptoms. To further this debate, research in which those subjects with an increased risk of asthma/allergy are clearly separated from those at 'low risk' of asthma would be very informative.

There is also controversy over the so-called 'hygiene hypothesis'. The US-based study of Ball *et al.* (2000) found a reduced risk of asthma if entry into daycare occurred at 0–6 months, but not if entry occurred at 12 months or older. Also, increasing numbers of older siblings was associated with a decreased risk of asthma. The study by Celedón *et al.* (2003) recruited only children with a parental history of atopy and found a significantly reduced incidence of asthma only in children with no maternal history of asthma who had attended daycare in the first year of life. Hence, it seems likely

[8] Institute of Medicine (IOM) (2000) *Clearing the Air: Asthma and Indoor Air Exposures,* Washington DC, USA, National Academy Press, available [March 2003] at http://www.nap.edu/books/0309064961/html/

that an effect on asthma related to attendance at daycare may only be found in certain children, depending on their underlying risk factors for asthma and/or atopy. Another factor is whether the commencement of attendance at daycare occurs sufficiently early in the child's life, although the critical stage in the child's life in this respect is uncertain.

There are many factors relating to the *in utero* environment and the time around parturition that have been linked causally with asthma. One of the most important issues is the link between maternal smoking during pregnancy and subsequent asthma in the child, especially as the child will often also be exposed to ETS during childhood. The study by Gilliland *et al.* (2001) aimed to address the problem of such confounding between smoke exposure *in utero* and after birth, and found that *in utero* exposure to maternal smoking was associated with increased asthma risk, when not accompanied by ETS exposure. However, this association achieved borderline significance only among children with no family history of asthma. Postnatal ETS exposure without maternal smoking during pregnancy was not associated with asthma. The review of Delfino (2002) also indicates that maternal smoking during pregnancy is of greater significance to asthma onset than ETS exposure in later life.

Interestingly, the study by Litonjua *et al.* (1998), which evaluated the links between asthma in children and asthma in the mother and the father separately, has demonstrated that childhood asthma is more strongly associated with history of asthma in the mother than with history of asthma in the father. Whether the underlying cause of this is genetic, immunological or environmental is a possible area for future investigation.

The increasing use of obstetric intervention during parturition has created cause for concern for a wide variety of reasons. A Finnish study (Xu *et al.*, 2000) has indicated potential links between asthma and the method of delivery used, with increased asthma risk associated with interventional deliveries, including Caesarian section. Other factors relating to *in utero* experience and/or events in labour and delivery have been associated with increased asthma risk; these include health complications during pregnancy, such as early or threatened labour, fetal malposition or malpresentation, antepartum haemorrhage and placental insufficiency. Maternal infections during pregnancy have also been associated with increased asthma risk in two studies, one British (Hughes *et al.*, 1999)* and one from Finland (Xu *et al.*, 1999)*.

Associations have been investigated between birth weight and other anthropometric measurements at birth. From the studies considered in this review, it is difficult to draw any conclusions with a high degree of confidence, but these are themes in asthma causation that may be worthy of further research.

The issue of whether the use of antibiotics causes asthma is unfortunately blurred by the possibility that pre-existing asthma may cause respiratory infections that are treated by antibiotics. Hence, if such an association is seen, it is not necessarily one of asthma causation by antibiotic exposure, but a retrospective association whereby asthma is being treated by antibiotics, but the underlying diagnosis has not yet been made. Furthermore, the study by Celedón *et al.* (2002), which excluded children treated with antibiotics in response to wheeziness, did not find an association between antibiotic use and transient wheeze. Another drug with a postulated association with asthma is paracetamol, but the evidence for this link is somewhat tenuous and requires further investigation. Although a study from New Zealand (Wickens *et al.*, 2001)* found no association between asthma and certain vaccinations, this is another area that may be worthy of further study.

Dietary factors have received a high degree of interest in relation to asthma causation. Certain aspects of the diet that have been discussed in relation to an increased risk of asthma have included a low intake of vitamins C and E. Other diets associated with increased risk of asthma are diets low in vegetables, milk, fibre and calcium. The review by Seaton *et al.* (2000) discusses the relationship between dietary fats and asthma. A diet high in fat intake has been suggested to be related to increased risk of diagnosis of asthma. The specific type of fat may also be of relevance, as a study is mentioned

in which high consumption of oily fish was found to be associated with reduced risk of asthma in children.

As the studies discussed in this report demonstrate, there is much controversy regarding the role of breastfeeding in asthma, with some evidence to indicate a reduced risk of asthma among breastfed infants, and other evidence to support the converse view. In examining this issue, there is also the possibility of a variation in the response to breastfeeding depending on other factors such as maternal asthma and atopy in the child.

Another issue connected with dietary factors is that of body weight. A link between asthma and overweight/obesity, often categorised by BMI measurements, has been proposed, and there are studies to support this view. However, some studies have found a link between overweight/obesity in females only. Other studies have found no association between increased body weight and asthma risk. There is the possibility that overweight/obese people may suffer more respiratory symptoms than those who are not overweight. They may then be more likely to receive a diagnosis of asthma from a physician, even if asthma is not the underlying cause of their symptoms.

This report has aimed to pick out some of the major theories relating environmental factors to an increased risk of asthma. The literature base in this area is very extensive, and a review of this type and scope can only hope to identify the key themes, rather than analyse their plausibility. One of the general points that can be made however, is that there is often a conflict of evidence in relation to a specific potential causative factor. While some of the discrepancies in the findings of such studies can be ascribed to differences in study design, outcome measures and study populations, a further possible explanation is that a particular factor may have different influences in different individuals, possibly related to their family history of asthma/atopic disease, or whether they personally are atopic. A key example of this may be the differences found in the studies related to breastfeeding and asthma risk, for example in the study by Wright *et al.* (2001)* the relationship between breastfeeding and asthma was modified by maternal asthma and atopy in the child.

To analyse the plausibility of the many risk factors associated with asthma (and of possible interactions between them), a more rigorous and extensive review of the literature is required, which will then allow systematic review of the studies identified. The collation of the data into a database format would facilitate analysis of the original studies. This would also help to identify studies that were sufficiently similar in terms of methodology and execution to enable meta-analysis technology to be validly applied. This would enable further information on the causative factors of asthma to be derived from the existing knowledge base. The ultimate goal of reducing asthma in the population, by taking control of environmental factors that promote, or mitigate against, its development, may then be more readily achievable.

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