RISK FACTORS FOR RESPIRATORY MORBIDITY IN PRIMARY SCHOOL CHILDREN IN MERSEYSIDE

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In 1991 a cross-sectional survey (n=2035) was performed with the primary objective of establishing whether there was increased respiratory morbidity in children (aged 5-11 years) who were living and attending school in an area with increased dust pollution (exposed area) compared to children in two control areas in Merseyside. Children were classified in to a number of respiratory symptom groups. The two commonest symptomatic groups were: a history of the symptom triad of cough with wheeze and breathlessness (CWB) and a history of the solitary symptom of excess cough (EC). CWB was related to predisposing factors such as maternal asthma, history of allergies and pre-term birth, in contrast EC was associated with adverse environmental factors such as attending school in the exposed area and damp in the home. In the exposed area the prevalence of doctor diagnosed asthma was 21.1%, CWB 13.5%, EC 14.5% and school absenteeism due to respiratory symptoms 21.2% which were significantly higher compared to the control areas (16.2%, 6.6%, 7.0% and 11.6% respectively). In 1993 environmental measures were taken to reduce dust levels. A second cross-sectional survey (n=4288) was performed in the same communities in 1993 in order to assess change in respiratory symptom prevalence. A 26.4% reduction in dust levels was observed during this period. The prevalence of CWB fell in the exposed area by 4.4% but that for EC remained the same.

The impact of maternal asthma on pre-term birth and the subsequent development of respiratory symptoms later in childhood was assessed. Maternal asthma and smoking during pregnancy had significant independent effects on the risk of pre-term birth (OR 1.49 and 1.35 respectively). Asthmatic mothers did not have an increased risk of delivering a small for gestational age baby. Pre-term birth increased the risk of the later development of CWB (OR 1.4), in contrast babies born small for gestational age were at reduced risk of developing CWB later in childhood. Thus, asthmatic mothers are at increased risk of delivering pre-term but not growth retarded babies, and it is pre-term birth that is associated with the subsequent development of CWB.

In 1995 a case-control study was undertaken in order to investigate associations between respiratory symptoms or lung function before and after exercise testing and biochemical nutritional status or dietary nutrient intake. Children (aged 7-11 years) were selected on the basis of available data from the 1993 survey. Cases were defined as either having a history of CWB (n-61) or a history of EC (n=69), and these children were matched by age, sex and consent to venepuncture with two symptom-free controls (n=148). Mean serum levels of vitamin E were significantly higher in children with EC compared to those with CWB ($p<0.05$) whether or not they had a family history of asthma. Vitamin E deficiency was less likely to occur in children with EC compared to those with CWB, indicating that children with milder respiratory symptoms had better antioxidant status. There was no difference in serum antioxidant status in children with and without exercise induced bronchoconstriction (EIB). Children with EIB had lower dietary intakes of vitamin C compared to those without EIB ($p<0.05$). Significant correlations were shown between indices of resting lung function in children with EIB and serum antioxidant levels.

Further studies are needed in order to assess the relationship between perinatal outcome and the subsequent development of respiratory symptoms and atopy. Antioxidants may have important influences on lung function in children. Improving the diets or supplementing those of pre-term babies, children with a genetic predisposition or those exposed to air pollution may contribute to the prevention of disease or reduce the severity of respiratory symptoms and bronchoconstriction.

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For John and Sophie

A cough and love cannot be hidden-
Latin Proverb

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Chapter One

Introduction and aims

1.1 Background to the study

The Liverpool docks are an importation route for a range of commodities. The dry bulk cargoes which are handled include grain, animal feeds, cement clinker and scrap metal. Until the late 1980s the importation and handling of coal at the Liverpool Docks was on a relatively small scale and intermittent in nature. In March 1988 the first major importation of petroleum coke was discharged and stockpiled at the North Bootle Docks, and in 1989 large scale importation and handling of steam coal began. The coke/coal was unloaded using mechanical grabs and stockpiled in goods yards for variable amounts of time and then transferred for transportation by road or train wagons. Residents in the vicinity, in some of the homes and one of the primary schools which were within 200 metres of the coal stockpiles, began complaining to the local council about black dust which was entering their homes, soiling surfaces, furnishings and washing. By April 1991 the council had received over 600 complaints. The volume of coal/coke being handled at the docks increased from half a million tonnes in 1988-89 to nearly two million tonnes in 1991-92 (Brabin 1992).

In 1993 one of the major coal handling companies began to operate a new process with the coal being unloaded from the ships via an enclosed chute. Coal stockpiles were moved further away from local housing and covered with tarpaulin sheets in order to reduce the amount of airborne coal dust.

During 1989 and 1990 South Sefton Health Authority received complaints from parents and teachers of two primary schools near to the Bootle Docks about what they considered to be a high incidence of 'asthma'. One school reported that more than one quarter of 5-6 year olds had been prescribed inhalers. A preliminary audit of general practice attendance in the Bootle dock area showed an increase in self reported ill health in the general population (Crombie 1990).

A Steering Committee was set up under the auspices of South Sefton Health Authority to investigate the concerns of parents and teachers. The primary objective of the Steering Committee was to determine whether there was a public health problem of excess respiratory morbidity in primary school children in the area adjacent to the Bootle Docks compared to children in areas elsewhere in Merseyside.

It is important to set the problem which emerged in North Liverpool in the wider context of the increased prevalence of childhood asthma in 'westernised' areas over the last 30 years. The reasons for this changing pattern of asthma are not understood but are likely to be multifactorial.

Hypotheses related to changes in the external environment such as the types of outdoor air pollution have been proposed. Until the 1960s industrial emissions, particularly of smoke and sulphur dioxide, were the main source of air pollution. More recently motor vehicle exhaust emissions have become a major source of the primary pollutants nitrogen dioxide, carbon monoxide and fine particulates and of the secondary pollutant ozone (Newman-Taylor 1995). Laboratory and epidemiological studies have shown strong associations between air pollutants and increased respiratory morbidity in asthmatic subjects (HMSO 1995a).

Changing patterns of indoor exposure to tobacco smoke and allergens have also been proposed. Environmental tobacco smoke is an important source of indoor air pollution. It has been estimated that 50% of children in the UK are exposed to passive smoke (Couriel 1995). There are difficulties in estimating the relative risk of respiratory morbidity from pre-natal and/or post-natal exposure of the foetus or child to tobacco smoke, as the majority of women who smoke during pregnancy continue to do so thereafter (Taylor and Wadsworth 1987).

Housing standards have changed in recent decades, homes have become less drafty and better insulated as double glazing, central heating

and wall to wall carpets have become more commonplace. Such changes create the ideal habitat for the now ubiquitous house dust mite, a perennial source of potent allergens. The amount of allergen exposure in the first few months of life may be a contributory factor in the development of asthma and allergic disease (Peat *et al* 1990). In addition, pollutants may enhance the passage of allergens across the respiratory epithelium (Molfino *et al* 1991).

Babies who are born prematurely and/or have low birth weight have improved survival due to recent advances in medical science. However, the lungs of premature babies have an incomplete compliment of surfactant and immature enzyme systems (Fardy and Silverman 1995), consequently these babies may be less able to cope with the effects of inhaled allergens and pollutants during the first weeks and months of life. Significant lung damage may be caused by such factors early in life which continue to have an effect later in childhood.

Changes in nutritional factors in recent decades may have altered host responses to oxidative damage (Seaton *et al* 1994). Dietary salt intake has been linked with asthma severity (Burney 1987) and changes in dietary oil consumption have been implicated in altered biological potency of inflammatory mediators (Fisher and Weber 1984). Reduced antioxidant vitamin intakes or greater host requirement for these nutrients may be important in the development of respiratory symptoms in susceptible individuals (Burney 1995).

1.2 Aims and objectives

The primary aim of this work was to determine the associations of environmental and host risk factors with respiratory symptoms in primary school children. The research was also undertaken in order to describe the pattern of asthma in a community of primary school children over a two year period.

The studies were undertaken in primary school children, the objectives were:

1. To determine whether there was increased respiratory morbidity in children living and attending school in an area of Merseyside with known increased levels of dust pollution.
2. To determine in these children the prevalence of the respiratory symptoms of cough, wheeze and breathlessness, either singly or in combination.
3. To identify risk factors associated with different respiratory symptom profiles.
4. To examine short-term temporal changes in the prevalence and severity of asthma and respiratory symptoms.
5. To determine incidence and recovery rates for different respiratory symptom profiles
6. To evaluate the impact of maternal asthma on pre-term birth and birthweight and the relation of these factors to the subsequent development of respiratory symptoms later in childhood.
7. To examine antioxidant vitamin status in relation to the different respiratory symptom profiles: excess cough as a solitary symptom and the symptom triad of cough with wheeze and breathlessness.
8. To determine the relationship between lung function and serum antioxidant vitamin levels in children with and without exercise-induced bronchoconstriction.

1.3 Thesis structure

Chapter two is a review of the relevant literature. **Chapter three** describes the study population and methods used in two cross-sectional respiratory health surveys conducted in 1991 and 1993 and the longitudinal follow-up of a cohort of children seen in both 1991 and 1993. Chapters four,

five and six describe the results of the cross-sectional surveys and the longitudinal survey. **Chapter four** examines the prevalence of respiratory morbidity in primary school children in the Bootle dock area which was exposed to coal dust compared to children from control areas elsewhere in Merseyside. **Chapter five** describes the risk factors associated with the different respiratory symptom profiles in these children. **Chapter six** examines the short-term temporal changes in respiratory morbidity in these children. **Chapter seven** evaluates the impact of maternal asthma on preterm birth and the subsequent development of respiratory symptoms later in childhood. **Chapter eight** describes the methods used in a case-control study conducted in 1995 in which lung function, atopy and nutritional status of children with different respiratory symptom profiles were compared. **Chapters nine and ten** describe the case-control study results, in particular the relationship between antioxidant nutritional status, respiratory symptoms and lung function. **Chapter eleven** is an overview of the results, the main conclusions and implications for future work.

Chapter Two

Literature Review

2.2 DUST POLLUTION AND ITS MEASUREMENT

2.2.1 Types of dust

There are a wide range of solid and liquid particles in the air. It is estimated that in rural areas there are between 5,000-10,000 particles per cm^3, this may rise to 30,000 per cm^3 if affected by road traffic at a distance of 1km (Rusos 1991). Relatively unpolluted urban air contains 10,000 particles per cm^3 and in polluted areas there may be up to 150,000 particles per cm^3 (HMSO 1995a).

Three types of particle are commonly cited in studies on the health effects of air pollution: Black smoke refers to fine suspended particulates arising from the incomplete combustion of fossil fuels. Total suspended particulates (TSP) refers to a mixture of airborne particles such as rock dust and combustion products. Particles of less than 10μm in aerodynamic diameter (PM_{10}), are referred to as "respirable particles" as they are able to deposit in small airways and alveoli. In many industrial areas there is a close relationship between particles and sulphur dioxide, for example in central Birmingham the correlation coefficient was equal to 0.73 (HMSO 1995b).

Particles greater than 2.5 μm are removed from the atmosphere by settling and rain, whereas very small particles (<1μm) can remain airborne for several weeks and in this time may travel large distances. Brauer and colleagues (1989) showed that indoor personal monitoring samples may contain as much of the very fine particulate fraction as encountered outdoors.

2.2.2 Sources of dust

In the UK in 1992 47% of black smoke came from road transport, 28% from domestic use, and the remainder from industrial sources (Holman 1994). Most of the urban particulate cloud originates from the combustion of fuels, particularly diesel. Particles from diesel exhausts are small (<0.5μm) and thus

have a high surface area to mass ratio. Small amounts of these particles provide a relatively large surface area on to which a variety of chemicals are adsorbed.

2.2.3 Measurement of particles

Historically the "smoke stain" method was used to measure concentrations of black smoke, the air sample being drawn through a filter paper and the reflectance of the resulting smoke stain measured, the concentration being obtained from a standard calibration curve. Over the last 30 years the composition of pollution has changed, as motor vehicles contribute more to atmospheric pollution and other methods of measuring pollution have become available. When the gravimetric method is employed a known volume of air is drawn through filter paper and the mass of particulate material is obtained by weighing. The PM_{10} sampling head is a device with a size selective orifice which allows particles of 10μm aerodynamic diameter or less to be captured. Whichever method of measurement is used the amount of particulate is expressed as $\mu g/m^3$, however smoke stain, gravimetric and PM_{10} measurements should not be directly compared (HMSO 1992).

2.3 EFFECT OF DUST ON RESPIRATORY HEALTH

2.3.1 Deposition of particles

When particles are inspired via the mouth and nose, they closely follow the movement of air in which they are suspended. The depth to which particles penetrate depends on their physical characteristics, (such as size, density, shape and aerodynamic diameter) and the volume of air in each respiration. Once a particle contacts an airway or alveoli wall it can not again

become airborne, thus it is deposited (Parkes 1995). Larger particles (3-20 μm) tend to follow the trajectory of their original path and are therefore likely to impinge on upper and conducting airway walls. They deposit by inertial impaction. In smaller airways air flow velocity is low, the force of gravity predominates and smaller particles (1-3 μm) deposit by sedimentation. Diffusion by Brownian motion is the method of deposition for very small particles (< 1 μm), this often occurs in very small airways and alveoli where the airway surface area is large and airflow velocity is very low (Parkes 1995, Gonda 1997). The mean sizes of particles deposited at different points in the respiratory tract are as follows; >10μm in the pharynx and larynx, 10μm in the trachea, 6μm in main bronchi, 3-5μm in the bronchioles and <3μm deposit in alveoli (HMSO 1992).

2.3.2 Clearance mechanisms

Clearance of deposited matter is due to the combined effects of mucus, cilia, phagocytosis and lymph drainage. In airway generations 1 to 15 it is cilia and mucus which are important for clearance. In smaller airways and alveoli phagocytosis by macrophages and lymph drainage are important. The mucinous lining of the airway traps and retains deposited foreign matter (Gilboa and Siberberg 1976). Ciliated epithelial cells beat beneath the mucus layer and are able to transport mucus into upper airways. In disease the mucinous layer may be affected by irritation and inflammation, deviation from its ideal elastic and viscous composition results in defective mucocilory clearance (Salathe *et al* 1997). Macrophages which line the smaller airways engulf foreign matter which is transported to lymph nodes which drain the lungs. Damage to the respiratory tract occurs if the rate of deposition exceeds the rate of removal or if particles are chemically reactive, e.g. cigarette smoke may contain relatively few particles but these are highly chemically active. Large particles may cause bronchitis, whereas small particles lead to

"alveolitis" and "small airways disease". The clearance mechanism may be altered by exposure to pollutants, high concentrations of SO_2 decrease the action of cilia and during such exposures particulate matter may become fixed more easily in the airway (Salathe *et al* 1997).

2.3.3 Effects of particulates on health

Studying the health effects of air pollution can be complicated as although we can readily define and categorise the actions and effects of individual pollutants, this may be artificial as interactions of pollutants may alter these effects on human health. The human host may also show considerable variation in response within and between individuals. Combinations of pollutants may act in three ways, additive, antagonistically or synergistically (HMSO 1992).

In addition to its interaction with other pollutants particulate matter itself can be biologically active, such as quartz which when inhaled in sufficient quantities leads to irreversible fibrosis of the lung (Richards *et al* 1984). If inhaled particles are allergenic the host response may lead to inflammation and oedema at the site of deposition e.g. pigeon fancier's lung.

2.3.3.1 Biological mechanisms

The mechanisms underlying the effects of particles on human health are not fully understood. Non-specific irritation of the airway may cause inflammation which could result in increased bronchial activity (Landau 1995). Interaction between pollutants and aeroallergens may be synergistic, such that when particles deposit on airway epithelium the passage of antigen across the epithelium may be enhanced. Seaton *et al* (1995) have suggested that penetration of very fine particles may cause inflammation which may in turn be associated with changes in the viscosity and coagulability of blood,

this may result in increased mortality and morbidity from cardiovascular disease.

2.3.3.2 Adults

Disease due to dust exposure in adults is often related to occupation, for example pneumoconiosis which is a group of diseases including silicosis, asbestosis, coal and talc workers' pneumoconiosis. Anthracosilicosis is due to exposure to a mixture of coal and rock dust containing free silica which may cause extensive fibrosis. Carbon or coal dust is relatively innocuous although in large quantities, as in coal miners it can lead to coal miners' pneumoconiosis and possibly to airway obstruction (Marine *et al* 1988). Such exposures are of a different order of magnitude to environmental exposures, and miners working on the surface do not develop disease, whereas those beneath ground exposed to more dust are more likely to develop disease. Levels of coal dust encountered in urban areas are usually low and do not have harmful effects.

Long term exposure to atmospheric particulates has been shown to be associated with increased risk of death from heart and lung disease. In a study of adults in Philadelphia the relative risk of death from cardiovascular disease and chronic obstructive pulmonary disease were estimated at 1.1 and 1.2 respectively (Schwartz and Dockery 1992). In a prospective study on over half a million adults from 151 metropolitan areas of the United States, the effects of particulate air pollution levels on mortality over a seven year period were evaluated. The adjusted risk ratio for all cause mortality for the most polluted areas compared to the least polluted for fine particulates was estimated at 1.17 (Pope *et al* 1995). In a review of epidemiological literature Dockery and Pope (1994) estimated that deaths from respiratory disease increased by 3.4% per 10 $\mu g/m^3$ increase in PM_{10}. Anderson *et al* (1996) in a report on the effect of pollution on daily mortality in London between 1987

1992 showed that the increased risk of all case deaths was 2.5% associated with an increase from the 10th to the 90th centile in "black smoke" (7-19 $\mu g/m^3$), which is below World Health Organisation guidelines.

2.3.3.3 Children

Evidence for an effect of particles, sometimes in combination with SO_2 and acid aerosols on lung function, respiratory symptoms and bronchial responsiveness in children comes mainly from panel or population studies. For panel studies individual children are selected in anticipation of fluctuations in pollution levels, each child is their own control, records of daily symptoms and PEF are taken. In whole population studies the period or cumulative prevalence of symptoms and reported asthma in areas with different pollution levels can be determined.

In a report from the Czech Republic the risk of post-neonatal respiratory mortality increased from the lowest to the highest exposure to total suspended particulates up to 10μm in size (TSP-10) quintile. It was estimated that an increase of 25 $\mu g/m^3$ TSP-10 increased post-neonatal mortality by a factor of 1.58 (Bobak and Leon 1992).

Lung function has been shown to be negatively correlated with levels of total suspended particulates (TSP) and black smoke (Dockery *et al* 1982, Hoek *et al* 1990, Roemer *et al* 1993). Mazur (1995) in a cross-sectional survey in Poland demonstrated reduced PEF in children living in an area of high dust, SO_2, NO_2 and lead compared to children from a non-polluted area. Peters *et al* (1996) in a study of winter type pollution (high SO_2 and moderate PM_{10} levels) on asthmatic children and adults in Eastern Europe reported increased symptoms and reduced PEF associated with increased SO_2 levels. An inverse relationship between PM_{10} and PEF has been widely reported, particularly in asthmatic children (Pope *et al* 1991, Pope and Dockery 1992, Neas *et al* 1995).

Braun-Farhlander *et al* (1992) reported increased symptoms associated with increased total suspended particulate levels in a study of Swiss pre-school children. Increased symptoms and bronchodilator usage have been associated with increased levels of PM_{10} pollution (Pope *et al* 1991, Roemer 1993, Romieu 1996). Buchdahl *et al* (1996) reported that acute wheezing episodes in children were associated with increased levels of summer haze (with high SO_2 and O_3 content). Conversely Hoek and Brunekreef (1995) in a study from the Netherlands did not show a relationship between reporting of symptoms and wide fluctuations in PM_{10} (11-135 $\mu g/m^3$) or O_3 (14-114ppb) levels.

Von Mutius *et al* (1992) suggested that long term exposure to increased levels of particulates and SO_2 in the former East German city of Leipzig could be responsible for the two-fold increased prevalence of bronchitis in children in Leipzig compared to Munich. This is supported by observations from the US Six Cities Study where associations were demonstrated between the occurrence of chronic cough and bronchitis and increased levels of particulates (Dockery *et al* 1989).

Molfino *et al* (1992), Wang *et al* (1992) and Tam *et al* (1994) reported that asymptomatic children living in highly polluted industrial areas had increased bronchial responsiveness compared to children from non-polluted areas. In contrast Ware *et al* (1986) and Von Mutius and colleagues (1994) showed no association between bronchial responsiveness and pollution.

2.3.4 Summary

1. The effect of particulate matter on the respiratory tract depends on the particle size, deposited dose, and its chemical and physical properties.
2. Occupational exposures can be large and lead to disease and death, e.g. asbestosis.

3. Environmental exposures are generally smaller, the effects are seen in both adults and children.
4. Prolonged exposure to increased levels of particulates rather than nitrogen dioxide or ozone have been associated with an increased prevalence of bronchitis and chronic cough in children.
5. Particulate exposure has been associated with increased mortality in neonates and adults, and with increased respiratory symptoms and decreased lung function in susceptible individuals.

2.4 ASTHMA AND RELATED ILLNESSES

2.4.1 Defining asthma

When seeking to establish the prevalence of asthma in epidemiological investigations it is important that the disease definition used is acceptable to facilitate comparisons between studies. The most widely agreed definition is based on the occurrence of 'wide variations over short periods of time in intrapulmonary airflow' (Clark 1993), although this is difficult to apply in the context of epidemiology. There are three commonly used measures for estimating the prevalence of asthma in cross- sectional population surveys. 'Doctor diagnosed asthma', respiratory symptoms (most commonly wheeze as a sole symptom or in combination with others) and bronchial hyperreactivity (BHR). BHR is not specific to asthma, thus it is not correct to compare its prevalence to period prevalence of 'doctor diagnosed asthma' or wheeze, although serial measures of BHR are useful as demonstrated by Peat and colleagues (1994). Workers in Australia have used the presence of BHR plus the 12 month period prevalence of wheeze as a definition of current asthma (Salome *et al* 1987, Toelle *et al* 1992).

Responses to questions about 'doctor diagnosed asthma' are influenced by parental recall, preference of medical practitioner and acceptance of the label (Peat *et al* 1992). A recent study showed evidence of differential recall of symptoms among children and their parents (Carey *et al* 1996). Historical comparisons of the cumulative prevalence of diagnosed asthma are flawed as under-diagnosis of asthma was common in earlier decades (Speight *et al* 1983). It is also difficult to quantify severity of asthma as some children have infrequent but severe attacks whilst others have frequent or more persistent milder attacks (Wilson *et al* 1997). Annual period prevalence of wheeze is the compromise measure of asthma now widely adopted in population surveys (Anderson 1989).

2.4.2.1 Prevalence in children

The prevalence of childhood asthma and symptoms associated with the disease have been extensively reported. The suggestion that the prevalence of childhood asthma in industrialised countries is rising (Anderson 1993) has been widely accepted. Surveys performed 10 to 15 years apart using the same methodologies have shown significant increases in the prevalence of asthma, wheeze and allergic disease in the UK and Australia (Burr *et al* 1989a, Robertson *et al* 1991, Anderson *et al* 1994, Peat *et al* 1994, Rona *et al* 1995).

There have been substantial increases in the annual period prevalence of wheeze which was reported to affect approximately 11% of children in the 1970s and 1980s (Lee *et al* 1983, Clifford *et al* 1989, Hill *et al* 1989a, Burney *et al* 1990, Rona *et al* 1995). More recent estimates of 12 month prevalence of wheeze range between 15% and 19% (Austin *et al* 1994, Strachan *et al* 1994) and 13% in pre school children (Luyt *et al* 1993). Ninan and Russell (1992) and Omran and Russell (1996) have reported the prevalence of wheeze in the previous three years to be 20% and 25% respectively in

Aberdeen school children. Rona *et al* (1995) reported that 13.5% of primary schoolchildren in England had occasional wheeze. The age-specific prevalence of cough has been reported to decrease with increasing age (Robertson *et al* 1991). In younger children cough is most often associated with viral infections in children older than five or six cough is often related to asthma where it can be the dominant symptom (Ninan 1993). Corrao *et al* (1979) reported cough as the sole presenting symptom of asthma in some patients. In children over the age of six the commonest aetiological factor underlying chronic cough is BHR (Hanaway and Hopper 1982, Lewis *et al* 1989). Recurrent cough may be a sign of worsening asthma, associated with bronchoconstriction and inflammation and may have nocturnal presentation (Martin *et al* 1991).

Diagnosed asthma prevalence has also increased. In the late 1970s an estimate of 1.7% was reported, but wheeze which responded to bronchodilator therapy affected 11% of the population which may have been a truer estimate of asthma prevalence (Lee *et al* 1983). More recently the prevalence of doctor diagnosed asthma has been reported to range between 13% and 20% in the UK (Austin *et al* 1994, Strachan 1994, Doull *et al* 1996, Omran and Russell 1996). Robertson *et al* (1991) in a study of seven year old school children in Melbourne in 1990 reported a period prevalence of wheeze of 23% and of diagnosed asthma of 46%. Duffy and Mitchell (1993) reported the annual period prevalence of wheeze as 14% in eight year old children in Queensland. Paediatric population studies from USA and Taiwan have also shown evidence of an increase in the annual prevalence of asthma (Weitzman *et al* 1992), wheezing and dyspnoea (Hsieh and Shen 1988). Studies of military recruits 10 to 20 years apart in Sweden, Finland and for a non-specified time in Israel have reported significant increases in the prevalence of diagnosed asthma (Aberg *et al* 1989, Haahtela *et al* 1990, Laor *et al* 1993).

There is evidence for a general trend to an increase in the prevalence of allergic disease and atopy (Taylor *et al* 1984, Aberg *et al* 1989, Ninan and Russell 1992). Sibbald and colleagues (1990) reported a doubling in the prevalence of atopy, assessed by skin testing, in an adult population between 1974 and 1988. Lewis *et al* (1996) reported a two-fold increase in the prevalence of eczema and hay fever in children. The prevalence of eczema has been reported to be higher in children from social class I and II compared to lower classes, and it has been suggested that factors associated with class such as home environment are important in the expression of disease (Williams *et al* 1994). The prevalence of recent wheeze, diagnosed asthma and BHR in Australia have increased in recent decades. Peat and colleagues (1994) studied children from two areas in New South Wales, ten years apart (1982-1992). They reported a two-fold increase in the period prevalence of wheeze and a similar increase in the prevalence of BHR, with no increase in the prevalence of atopy (approximately 30%), most of the observed increases in BHR being among atopics.

2.4.2.2 Geographical variations

Comparative studies between the UK and New Zealand suggest a higher prevalence and severity of asthma in New Zealand (Mitchell *et al* 1990, Barry *et al* 1991). Pearce *et al* (1993) reported that asthma prevalence and severity were highest in Australia, lowest in Germany and intermediate in the UK. Burr *et al* (1994) reported that the prevalence of wheeze was similar in New Zealand, Wales and South Africa and lower in Sweden, although the prevalence of allergic disease followed a different pattern being highest in Sweden. The increases in the prevalence of asthma and wheeze in the UK and Australia are relatively similar although the prevalence is higher in Australia compared to the UK (Baumann 1993)

Crain *et al* (1994) reported a higher prevalence of asthma among inner city children in the Bronx compared to national prevalence estimates for the US (Weitzman *et al* 1992). Carter-Pokras and Gergen (1993) reported that current asthma prevalence in children, aged six months to 11 years, varied between ethnic groups and geographical location. In New York City 11.2% of Puerto-Ricans had current asthma, 2.7% of Mexican-Americans in the South West, and 5.2% of Cubans in Miami compared to 3.3% of non-Hispanic whites and 5.9% of non-Hispanic blacks from a US national sample. Schwartz *et al* (1990) reported that, after adjusting for social factors, black race was a significant risk factor for asthma and wheezing illness in a national sample of children from the US. Analyses of the 1958 and 1970 British Birth Cohorts showed no regional differences in lifetime asthma or annual wheezing prevalence (HMSO 1995a). Strachan *et al* (1994) did not show any urban-rural difference in the annual prevalence of wheeze although attacks of wheeze were less frequent in rural areas. In contrast, Austin and colleagues (1994) reported that in the Highlands of Scotland the highest prevalence of lifetime wheeze and exercise induced bronchoconstriction was in children from the Isle of Skye, the most rural area in the study. These observations do not support the suggestion that asthma and wheeze are more common and/or more severe in urban compared to rural areas.

It has been reported that the prevalence of exercise-induced bronchoconstriction is higher in urban compared to rural areas in South Africa (van Niekerk *et al* 1979), Zimbabwe (Keeley *et al* 1991) and Ghana (Addo Yobo *et al* 1997). Thus factors associated with wealth, lifestyle and housing as well as a genetic predisposition are important in the expression of asthma. Children from affluent urban areas of developing countries may be exposed to more allergens as it was reported that house dust mite allergen was found for the first time in homes in Papua New Guinea where there had been considerable 'Western' influence (Dowse *et al* 1985). Asthma prevalence has

been reported to be low in remote areas, such as the highlands of Papua New Guinea (Anderson 1974), in Native American communities (Herxheimer and Shaefer 1974), Savanna region of Nigeria (Warrell *et al* 1975), rural Gambia (Godfry 1975) and in the Pacific Island of Tokelau (Waite *et al* 1980).

Strachan and colleagues (1994) in a report on regional variations in asthma prevalence in Britain suggested that area of birth was less influential than area of residence, thus current environment rather than genetics gives rise to geographical variations in the occurrence of disease. The evidence that immigrant populations show an increased prevalence of asthma when they change lifestyle or environmental exposures by moving to 'Westernised' areas is inconsistent. In a study of second generation immigrants it was reported that asthma prevalence resembled that of the community where they lived compared to asthma prevalence in their parents which was similar to that in the community from which they came (Smith *et al* 1971). Similarly, Hurry *et al* (1988) in a study of school children in Sydney reported that when children migrate after the first year of life the prevalence of asthma resembles that of the community from which the child came. Whilst migration *in utero* is associated with prevalence of the community into which the child is born. There were no differences in asthma prevalence among children born in the Pacific island of Tokelau who subsequently migrated to New Zealand and children of Tokelauan descent born in New Zealand (Waite *et al* 1980). Pararajasingam *et al* (1992) reported that the prevalence of asthma symptoms was lower in Asian compared to European children in Southampton. Conversely, children of West Indian ethnicity born in UK had higher prevalence of asthma and wheeze than those born overseas (Smith *et al* 1971). A study of adult Asian immigrants in London showed later onset of asthma (which often occurred after moving to Britain) than adults of Asian descent born in the UK (Partridge *et al* 1979).

2.4.3 Natural history

There are sex differences in the occurrence of asthma and wheezing illness, in the first decade of life as boys are more likely to develop disease than girls (Horwood *et al* 1985, Ownby 1990, Martinez *et al* 1991). Yunginger *et al* (1992) showed evidence of an increase in the incidence of asthma in children in the US between 1964 and 1983, and that boys had a higher incidence and earlier onset of disease compared to girls. A series of studies have shown that abnormal lung function soon after birth, before symptoms had occurred was associated with small airway size which was associated with subsequent wheezing illness in boys but not in girls (Martinez and colleagues 1988, 1991). It has been suggested that boys are genetically predisposed to being born with smaller airways than girls, and that this is the cause of their increased susceptibility to asthma in the first few years of life. The nature of this possible genetic effect has yet to be defined (Le Souef 1995). Taussig *et al* (1982) demonstrated that forced expiratory flows are lower in new-born boys than girls. The incidence of respiratory illness and atopy are higher in male infants compared to females (Magnussen *et al* 1986, Gold *et al* 1989). Martin *et al* (1980) and Strachan *et al* (1994) reported that by adolescence the sex differential in the prevalence of wheezy illness had largely disappeared. Forced expiratory flow rates are equal in late adolescence (Polgar and Weng *et al* 1979).

Williams and McNichol (1969) showed that ten year old children with persistent symptoms were more likely to have had onset before the age of three compared to children whose symptoms cleared up. Martinez and colleagues (1995) who followed a cohort of children from birth identified two different groups of wheezers. Firstly, children who were non-atopic who had wheeze at three years of age and abnormal lung function in infancy but neither at six years of age. These children were more likely to have mothers who smoked. Secondly, children who had wheezing before the age of three

which persisted at six. This group of children were more likely to have a family history of asthma, be atopic and have normal lung function in infancy, but not at age six. Later age of onset of disease has been reported in developing countries where between 16% and 31% of adults with asthma had onset of disease before the age of 20 (Anderson 1974, Warrell *et al* 1975). Studies from England and Singapore during the same time period reported that 63% and 86% of adult asthmatics had disease onset before 20 years of age (Mun 1972, Pepys 1973).

Park *et al* (1986) and Kelly *et al* (1987) characterised the unstable nature of asthma by showing that some children who 'grew out' of their asthma relapsed later in life whilst some children who had persistent symptoms during adolescence later remitted. Nakadate and Kagawa (1992) demonstrated that abnormal peripheral lung function in children with a history of asthma may persist even if they have been in clinical remission for several years. Roorder and colleagues (1993, 1994) reported that childhood FEV_1 was the only significant predictor of lung function in adults. Three quarters of moderate to severe asthmatic children had symptoms which persisted into adolescence, and that young women were more likely to have symptoms and bronchial hyperreactivity than young men. This is supported by a report from a cohort study which followed children from age seven, which showed that as adults women were more likely to have asthma than men (Jenkins *et al* 1994).

Mann *et al* (1992) showed that wheeze in adulthood was related to wheezing illness in childhood and smoking in adulthood. Similarly, analysis of the 1958 Birth Cohort data has shown that relapse of wheeze at age 33 to be associated with cigarette smoking as adults and a history of hayfever, eczema or allergic rhinitis (Strachan *et al* 1996a). It has also been shown that young adults with a recent history of wheeze had significantly reduced lung function compared to those without symptoms. Of those who had had persistent

wheeze throughout childhood and adolescence there were greater decrements in lung function which were less reversible (Strachan *et al* 1996b).

2.4.4 Summary

1. The definition of asthma used in epidemiological setting varies between studies, thus making comparisons difficult. A mutually acceptable definition of asthma is desirable.
2. The prevalence of childhood asthma in industrialised countries has increased over the last 30 years. In urban areas of developing countries asthma prevalence is higher than in rural communities.
3. Geographical variations in asthma prevalence and studies of migrant populations suggest that environmental as well as genetic factors are important in the expression of the allergic phenotype.
4. Onset of wheezing illness before the age of three is more often associated with persistent symptoms throughout childhood. Lung function and respiratory symptoms in adults are influenced by childhood allergies and respiratory health.

2.5 OTHER ENVIRONMENTAL RISK FACTORS

2.5.1 Indoor

2.5.1.1 Environmental Tobacco Smoke (ETS)

In a recent review it was estimated that approximately 50% of children in the UK are exposed to passive smoke (Couriel 1994), and that ETS from a mother has a greater impact on the child's health than that from a father even though a lower proportion of women smoke (Cook *et al* 1994). This is partly due to the greater amount of time mothers generally spend with their infants.

The dose of cigarette smoke is related to the strength, type, number of cigarettes smoked, proximity of the child to the smoker, room size and ventilation.

The respiratory tracts of children are particularly vulnerable to the effects of inhaled toxins as they are physiologically and immunologically immature and are rapidly developing, thus any damage to the lung during childhood may affect growth and function thereafter. It is difficult to separate out the effects of intra-uterine exposure to cigarette smoke and post-natal passive smoking, as 90% of mothers who smoke during pregnancy still smoke five years later (Taylor and Wadsworth 1987, Frischer *et al* 1992).

Cotinine is the main metabolite of nicotine, and measurement of cotinine in serum, saliva and urine can be used as an objective biological marker of recent cigarette exposure. Duff *et al* (1993) showed that children aged less than two years had higher levels of salivary cotinine compared to older children, and that passive smoke exposure was associated with acute wheezing illness, thus younger children may be at greater risk of morbidity due to ETS than older children. Cotinine measurement is more sensitive than questionnaire responses when trying to assess ETS exposure in the home. The lack of sensitivity of questionnaire responses may explain some of the negative observations between respiratory symptoms and passive smoke. For example, Cook and colleagues (1993) showed that salivary cotinine was inversely associated with indices of lung function, but that reduced lung function was not statistically associated with questionnaire responses about smokers in the home.

It has been reported that children exposed to passive smoke are at increased risk of respiratory infections. Wright *et al* (1991) reported a four-fold increased risk of bronchiolitis and that this infection was more likely to be contracted at an earlier age. Increased hospital admissions due to respiratory problems in infants exposed to ETS have been reported (Harlap and Davies

1974). Stoddard and Miller (1995) reported that children of mothers who currently smoked were more likely to have wheezing respiratory illnesses than children of non-smoking mothers. The authors estimated that 7.5% of asthma or wheezing respiratory illness are attributable to maternal smoking. Analysis of 1958 Birth Cohort data showed parental smoking to be associated with the occurrence of all wheezing illnesses (Strachan 1995). Somerville *et al* (1988), Chinn and Rona (1991) and Brabak *et al* (1995) have shown associations between passive smoke exposure and the occurrence of respiratory symptoms in children and that symptoms were related to the number of cigarettes smoked by parents. Ware *et al* (1984) showed a 20-38% increased risk of respiratory illness and symptoms associated with current maternal smoking in the US Six Cities Study of respiratory health in children aged 6-9 years. Associations between passive smoke, wheeze and asthma have been widely reported (Burr *et al* 1989b, Weitzman *et al* 1990, Wright *et al* 1991, Neas *et al* 1994, Lindfors *et al* 1995). Conversely Schenker *et al* (1983) did not show an effect of passive smoking on asthma, respiratory symptoms or BHR.

The evidence for an effect of passive smoke on BHR is equivocal. Strachan *et al* (1990) showed that small airway function was inversely related to cotinine measurements but exposure to passive smoke did not increase BHR assessed by a free running exercise test. In contrast Martinez and colleagues (1988) reported passive smoking to be associated with increased BHR to inhaled methacholine in asthmatic and non-asthmatic boys but not girls, independently of the presence of atopy. Frischer *et al* (1992) showed that current maternal smoking was not associated with increased risk of BHR but exposure to cigarette smoke during the first year of life in asthmatic and non-asthmatic seven year old children was associated with increased risk of BHR assessed by exercise testing. Agudo and colleagues (1994) reported that exposure to cigarette smoke from the mother was associated with

increased risk of exercise induced bronchoconstriction, and that more recently exposed children were at greater risk. Magnussen *et al* (1993) investigating acute effects of ETS on mildly asthmatic children reported significant reductions in FEV_1 at rest but not after exercise. Murray and Morrison (1986, 1989, 1990) showed that asthmatic children with smoking mothers had 13-23% lower FEV_1 and increased bronchial responsiveness to histamine compared to asthmatic children of non-smoking mothers. Newborns of mothers who smoked during pregnancy were more responsive to histamine than infants of mothers who did not smoke during pregnancy (Young *et al* 1991). Prolonged bronchial responsiveness in children after acute cigarette smoke challenge has also been shown. Cigarette smoke is an adjuvant for aeroallergens; children of parents who smoke have raised cord IgE and total IgE in childhood (Kjellman 1981, Magnussen 1986, Kershaw 1987). Ronchetti *et al* (1992) reported that exposure of children to ETS and specific allergens may enhance allergenic sensitisation.

Ehrlich and colleagues (1992) observed that passive smoking was related to asthma diagnosis but not acute exacerbations, this led them to suggest that passive smoking is linked to hyperreactivity rather than bronchospasm. Conversely Chilmonczyk *et al* (1993) showed high urinary concentrations of cotinine in children to be associated with acute exacerbations of asthma.

Wang and co-workers (1994) showed a decrement in lung function growth associated with maternal smoking which they concluded was partly due to intrauterine and early life exposure as well as current smoking. Tager *et al* (1983) in a prospective study reported that maternal smoking lowered FEV_1 growth by 7-10% over a seven year period. Gold *et al* (1996) reported that active smoking among adolescents was associated with reduced lung function growth, particularly in girls. A report by Strachan (1990) suggested

small airways damage associated with ETS may lead to later respiratory problems.

2.5.1.2 Gas cooking

The use of gas for cooking is associated with the production of NO_2 which may accumulate in kitchens without adequate ventilation. NO_2 has low solubility and greater than 60% of inhaled NO_2 is deposited in the lung.

Melia *et al* (1977, 1979 and 1988) in a series of epidemiological studies reported that respiratory symptoms in primary school children are associated with a combination of gas for cooking and the use of kerosene heaters, but that this association may disappear as children grow older. In support of this Strachan and Carey (1995) reported that gas for cooking was not associated with wheeze in adolescents. Von Mutius *et al* (1996) reported a reduced risk of hayfever, atopy and BHR in 9-11 year old children living in homes with wood or coal stoves and heating compared to children from homes where gas or another fuel was used.

Laboratory studies on the effects of NO_2 either on its own or in combination with another pollutant or known trigger of asthma are inconsistent. Inhalation of NO_2 at very high concentrations (2250-5500 ppb) has been shown to cause increased airway responsiveness in asthmatics and inflammatory influx in healthy individuals (Sandstron *et al* 1991), though it is unlikely that such concentrations would be attained in the atmosphere (HMSO 1995a). Tunnicliffe and colleagues (1994) showed that inhalation of NO_2 enhanced the response to inhaled house dust mite allergen in subjects with mild asthma. *In vitro* studies of bronchial epithelium exposure to 400-800 ppb NO_2 showed that cell dysfunction was caused (Devalia *et al* 1993). It has been suggested that NO_2 may increase the permeability of the bronchial mucosa to allergens thus lowering the threshold for sensitisation (Devalia *et al*

1994). In contrast, Koeng *et al* (1985) and Linn *et al* (1986) reported no effects of inhaled NO_2 on lung function or airway responsiveness in asthmatic subjects. Such reported variations in responses to NO_2 in laboratory studies have directed attention toward the identifying determinants of susceptibility including, age, pattern of exposure, underlying disease and antioxidant status.

In a recent review of the literature a committee of the environmental and occupational health assembly of the American Thoracic Society (1996) concluded that indoor levels of NO_2 due to gas cooking are associated with an increased risk of respiratory illnesses and symptoms in children. Patients with asthma or mild COPD may be at greater risk of the detrimental effects of NO_2 on lung function.

2.5.1.3 Aeroallergens

Allergens which affect asthmatic individuals have common characteristics. They are small and so easily respirable, have potent enzyme activity and either they are found in high concentrations or there is perennial exposure. Sears *et al* (1993a) reported that 80-90% of asthmatics are sensitive to at least one common allergen. Indoor allergens are important as most people spend the majority of their time indoors. Holt and colleagues (1990) suggested that exposure to allergens in infancy when the immunological system is immature may lead to the production of memory T cells. When re-exposure to that allergen occurs later in life specific IgE antibodies are produced. Peat *et al* (1990) reported that children who were sensitised to allergens early in life were more likely to develop asthma than children who were exposed later in childhood. There is some evidence that aeroallergen exposure *in utero* may be associated with sensitisation later in life (Warner and Warner 1995).

House Dust Mite

House dust mite allergen (*Dermatophagoides pteromyssinus* allergen I, *Der p* I) has been shown to be an important risk factor for bronchial hyperresponsiveness and respiratory symptoms (Sporik *et al* 1992, Sears *et al* 1993b). House dust mite thrives in conditions of low ventilation and high humidity (Wickman *et al* 1994), dampness and soft furnishing (Munir *et al* 1995), it is ubiquitous, perennial and releases the potent protease *Der p* I. Sporik *et al* (1990) showed that the development of wheeze was related to the amount of *Der p* I in a child's bed. Exposure to *Der p* I in the first year of life was associated with a positive skin test at one year of age (Warner *et al* 1991). Peat and colleagues (1994) showed a four to five-fold increase in house dust mite concentrations and significant increases in BHR in children in two Australian towns over a ten year period. The authors suggested that increases in airway hyperresponsiveness (but not atopy) may be due to increased allergen load in a child's environment or that factors which protected the airways of earlier generations of children have changed.

Furred pets

It has been shown that sensitisation to cats and dogs is more likely if a child is exposed during the first year of life (Vanto *et al* 1983). Cats are a well recognised source of allergen associated with asthma (Warner *et al* 1991, Sears *et al* 1993b, Lindfors *et al* 1995) particularly in areas where house dust mite levels are low, such as at high altitude (Sporik *et al* 1995). Warner *et al* (1991) showed that exposure to cat and dog allergens during the first 12 months of life was associated with positive skin tests at age one. In a comparative study of asthma and wheezing in New Zealand, South Africa, Wales and Sweden, Burr and co-workers (1994) showed that pet ownership was associated with wheezing illness in childhood except in Sweden where cat ownership was rare compared to New Zealand.

Mould

Many studies that have reported an association between damp or mould in the home and respiratory symptoms in children have relied solely on information from questionnaires (Martin *et al* 1987, Andrae *et al* 1988, Brunekreef *et al* 1989, Dales *et al* 1991). The validity of these observations in the absence of objective measures has been questioned (Strachan 1988). He concluded that the presence of damp or mould in the home may be a determinant of reporting of respiratory symptoms and thus a potential source of bias. Burr and colleagues (1988) based the association between asthma and mould in the home on the increased prevalence of positive radioallergosorbant tests to *Penicillium spp.* among subjects with mould in their homes. Waegenaekers *et al* (1989) and Verheoff *et al* (1992) showed higher concentrations of airborne fugal spores in damp homes. There is also clear evidence of a link between damp in the home and dust mite infestation (Blythe *et al* 1976, Burr *et al* 1980, Korsgaard 1983, Wickman *et al* 1994). It is plausible that the presence of house dust mites which produce strong allergens, and mould spores are involved in the development of allergic sensitisation and symptoms related to asthma (Burr *et al* 1985, Platts-Mills *et al* 1989, 1992, Verhoeff *et al* 1995). Warner and Warner (1995) suggested that *Alternaria spp* has a more rapid release of allergens than other moulds and thus is associated with severe responses in sensitive individuals.

2.5.2 Outdoor pollution

2.5.2.1 Motor vehicle and industrial emissions

Motor vehicle emissions contain particles, volatile organic compounds (VOCs), oxides of nitrogen (NO_x) especially NO_2, lead and sulphur oxides (SO_x). Ozone (O_3) is a secondary pollutant resulting from the action of sunlight

on VOCs and NO_2. In recent years there has been a decrease in the amount of pollution from the combustion of fossil fuels, especially SO_2 and urban smoke and an increase in pollutants originating from motor vehicles, in particular NO_2, O_3 and particulates from diesel exhausts (Newman-Taylor 1995).

Laboratory studies on the effects of individual pollutants have given conflicting results, which may be due to modifying effects of pollutants over each other. Koeng *et al* (1991) showed that the effect of SO_2 was modified by O_3, and Molfino *et al* (1991) showed that O_3 can interact with pollen allergen to reduce the concentration of allergen needed to provoke an asthmatic response. NO_2 has been shown to potentiate the effects of SO_2 on respiratory function in chamber studies (Jorres and Magnussen 1990). Devalia and colleagues (1994) demonstrated that a combination of NO_2 and SO_2 which could be encountered in heavy traffic enhanced the airway response to inhaled allergens in adults. It has also been reported that inhalation of NO_x and O_3 leads to airway inflammation and increased responsiveness in asthmatic adults. Frischer *et al* (1993a) showed evidence of increased inflammation in asthmatic children exposed to increased levels of ozone.

Several panel and population studies have reported negative correlations between lung function and atmospheric ozone levels in asthmatic and non-asthmatic children (Lebowitz *et al* 1985, Lioy *et al* 1985, Specktor *et al* 1988, Krzyzinowski *et al* 1992, Neas *et al* 1992). Increased levels of ozone in combination with acid aerosols have also been associated with reduced lung function (Dockery *et al* 1982, Kinney *et al* 1989, Raizenne *et al* 1989, Higgins 1990, Berry *et al* 1991, Specktor 1991, Studnicka *et al* 1995). Ozone levels have also been associated with respiratory symptoms and exacerbations of asthma (Ostro *et al* 1994, Romieu *et al* 1995, Buchdahl *et al* 1996). Sulphur and nitrogen dioxides have been associated with lung function (Lebowitz *et al* 1985, Peters *et al* 1994), respiratory symptoms (Rutishauser *et*

al 1990, Buchdahl *et al* 1996) and bronchial reactivity (Soyseth *et al* 1995a, 1995b) in children.

In contrast to these observations Kurata *et al* (1976), Stebbing *et al* (1976), Vedal *et al* (1987) and Brunekreef *et al* (1991) have not demonstrated any effect of O_3, SO_2 or NO_2 on lung function or respiratory symptoms in children. Dodge and colleagues (1985) reported a lower prevalence of wheeze and dyspnea in children living near a smelter works (with increased levels of SO_2) compared to those living in a non-polluted area. A recent review (Burr 1995) concluded hat air pollution episodes may exacerbate pre-existing respiratory symptoms in children.

2.5.2.2 Weather

Asthma epidemics associated with thunderstorms have been reported in the UK (Packe and Ayers 1985, Murray *et al* 1994, Celenza *et al* 1996, Thames Regions Accident and Emergency Trainees Association (TRAETA) 1996) and Australia (Bellomo *et al* 1992). It has been suggested that such episodes are related to the release of aeroallergens due to changes in atmospheric pressure and a fall in temperature. During the summer of 1994 in the south of England, of people treated at the Accident and Emergency department over 40% had never had an asthma attack before. It was suggested that those people were particularly sensitive to high levels of grass pollen (TRAETA 1996). Celenza *et al* (1996) suggested that patients with a previous history of asthma had attacks triggered by different factors compared to those who attended hospital with no prior history of asthma.

2.5.2.3 Aeroallergens

Bjorksten *et al* (1980) suggested that month of birth may be important in sensitisation to birch pollen. In a study of Cedar tree pollen in Japan hayfever was reported by 1.7% of families living in rural mountainous regions,

5.1% of families living near forests with no traffic, 8.8% of those living in urban areas near to forests, and 13.2% in those living next to inner city roads. It was suggested that pollution from motor vehicles may enhance sensitisation to pollens (Ishizaki *et al* 1987). Exposure to grass pollen and *Altenaria* spores, often in dry agricultural areas has been shown to cause exacerbations of asthma, peaks in exposure to these occur under specific meteorological and seasonal conditions (O'Hollaren 1991, Bellomo *et al* 1992, Suphioglu *et al* 1992, Knox *et al* 1993, Peat *et al* 1993). A report from Barcelona (Anto *et al* 1989) showed that outbreaks of asthma in the city in 1985 and 1986 coincided with the unloading of soybeans in the city harbour when the wind was blowing inland. One of the two silos into which the soybeans were unloaded did not have a filter and soybean dust was released into the air. Analysis of air samples from epidemic days showed quantities of soybean fragments. It was concluded that the inhalation of allergenic soybean dust was responsible for the outbreaks of asthma. Filters were fitted to the silos and this resulted in the prevention of soybean-epidemic asthma (Anto *et al* 1993).

2.5.3 Summary

1. Passive smoke exposure while *in utero*, during infancy and childhood is associated with impaired lung function development, an increased risk of respiratory infections and of symptoms which are more likely to occur at an earlier age.
2. Oxidising pollutants such as NO_2 and O_3 have detrimental effects on lung function in children and adults with pre-existing lung disease.
3. Changes in housing in recent decades have led to increased indoor levels of house dust mite allergen. Allergen exposure in early life is associated with a higher prevalence of atopy.
4. Pollutants such as SO_2, O_3 and particulates may potentiate the action of aeroallergens leading to increased expression of atopy.

2.6 HOST RISK FACTORS

2.6.1 Genetic

Disentangling genetic and environmental determinants of asthma has proven difficult in the context of epidemiological studies, though it is clear that asthma, allergic disease and atopy run in families. It has been shown that the risk of a child having allergic disease or atopy is higher if both parents are affected compared to one parent, which in turn is a greater risk to the child than neither parent having allergies or being atopic (Kaufman and Frick 1976, Blumenthal 1986, Ownby 1990). Asthma and atopy are related, and studies have shown that raised IgE levels are associated with asthma and BHR (Burrows *et al* 1989, Sears *et al* 1991). In recent years studies involving the use of molecular genetic techniques have strongly implicated the involvement of the gene for the high affinity IgE receptor site, on mast and airway cells, in the process of atopy. Initial work by Cookson *et al* (1989) and Young *et al* (1992) showed that the gene locus chromosome 11q13 was associated with the IgE response found in allergic disorders. Furthermore, it was demonstrated that transmission of the 11q13 gene only affected offspring if derived from the mother (Cookson *et al* 1992). It has been reported that mutations of the high affinity IgE receptor gene on chromosome 11q13 or a closely related gene influence the occurrence of bronchial hyperresponsiveness (Shirakawa *et al* 1994, van Hewerden *et al* 1995). Postma *et al* (1995) reported that one or more genes located on chromosome 5q31-q33 are associated with a susceptibility to asthma. It seems that many genes are involved in asthma and allergic disease, these may include those for β_2-adrenoreceptors and interleukins (Reihsaus *et al* 1993).

2.6.2 Intrauterine growth and maternal factors

Impaired foetal growth represented by low birth weight may exert some influence on the generation of abnormal lung function. Barker and colleagues (1991) associated low birth weight with decreased lung function later in life. Godfrey *et al* (1994) showed that disproportionate foetal growth represented by larger head circumference in relation to length at birth was associated with higher total IgE levels.

There is considerable evidence that smoking in pregnancy reduces birth weight (MacMahon *et al* 1966, Comstock *et al* 1971, Naeye 1978). Cigarette smoke exerts its effects on the developing foetus by leading to intrauterine hypoxia resulting from the formation of carboxyhaemoglobin which reduces the oxygen carrying capacity of the blood. Catecholamine release from the adrenal glands causes vasoconstriction in the uterus and reduced placental blood flow, thereby reducing nutrient and oxygen delivery to the foetus (Quigley *et al* 1979, Abel 1980). Differences in the ultrastructure of placentas from smoking and non-smoking mothers may also contribute to decreased placental blood flow (Asmussen 1980). It has been shown that the systemic and pulmonary vasculature of the foetus and the neonate are affected by hypoxia, carbon monoxide and nicotine (Holsclaw and Topkham 1978, Collins *et al* 1985, Maritz and Woolward 1992). Cigarette smoke contains nicotine and toxins which pass to the foetus either across the placenta or by absorption from amniotic fluid. Ostrea *et al* (1994) showed that the meconium of newborns whose mothers smoked during pregnancy had significantly higher levels of cotinine compared to meconium from babies whose mothers were from a non-smoking environment. There were similar levels of cotinine in the meconium of babies whose mothers were 'light' smokers and mothers exposed to passive smoke. Bottoms *et al* (1982) showed elevated levels of thiocyanate, a toxic by-product of cigarette smoke, in cord serum from babies of mothers who were regularly exposed to ETS

compared to babies of mothers from non-smoking environments. It has also been reported that exposure to cigarette smoke *in utero* adversely affects lung development and leads to decrements in lung function (Stick *et al* 1996).

Several studies have shown that smoking during pregnancy increases the risk of pre-term labour (<37 weeks gestation) and low birth weight (<2501g) (Brooke *et al* 1989, Wen *et al* 1990, Fox *et al* 1994, Conter *et al* 1995, Cornelius *et al* 1995, Peacock *et al* 1995). Conter *et al* (1995) showed that the magnitude of the effect was related to the number of cigarettes smoked. Wen *et al* (1990) and Fox *et al* (1994) also reported that the effect of smoking during pregnancy on birthweight increased with increasing maternal age.

Young *et al* (1991) and Hanrahan *et al* (1992) reported that abnormal lung function was related to ETS exposure *in utero*. Maternal smoking during pregnancy has been reported as a risk factor for wheeze (Lewis *et al* 1995, Strachan 1995), asthma (Sears *et al* 1996) and impaired lung function in childhood (Cunningham *et al* 1994, Stick *et al* 1996). Children born with low birth weights have been shown to be at increased risk of developing asthma or respiratory symptoms, reduced lung function and increased airway responsiveness (Chan *et al* 1988, 1989a, Seidman *et al* 1991, Kitchen *et al* 1992, Rona *et al* 1993, McLeod *et al* 1996).

Studies on the effects of passive smoke on birth weight and gestational age are inconsistent. Ahlborg and Bodin (1991) reported that passive exposure to cigarette smoke in the work place was weakly associated with pre-term delivery but not low birth weight. Martin and Bracken (1986), Rubin *et al* (1986), Lazzeroni (1990), Fortier (1994) and Zhang and Ratcliffe (1996) showed that passive smoking was associated with an increased risk of reduced birth weight. Conversely Brooke *et al* (1989) and Ogawa *et al* (1991) did not find an association between passive smoking and reduced birth weight. Martinez *et al* (1992) reported that lower maternal age may be a risk

factor for wheeze in the first year of life though this effect may be explained by biological and social factors related to maternal age.

2.6.3 Premature birth

The bronchial and uterine smooth muscle hypothesis was proposed following the observation that bronchoconstriction after provocation challenge was more common among women who had delivered pre-term (Bertrand *et al* 1985). This has been supported by observations of Doucette and Bracken (1993) and Kramer *et al* (1995) who showed that women with a history of asthma were at increased risk of pre-term delivery. In contrast, Rona *et al* (1993) and Schatz *et al* (1995) did not find an association between maternal asthma and pre-term delivery, although in the Schatz study the women had well controlled asthma. The hypothesis is further supported by the use of similar pharmacological agents in the treatment of asthma and pre-term labour, such as β_2-agonists. Agents such as prostaglandin $F_{2\alpha}$ which cause bronchial smooth muscle to contract also cause contraction of uterine smooth muscle.

Pre-term birth has been reported as a childhood risk factor for asthma or respiratory symptoms (Rona *et al* 1993, von Mutius *et al* 1993, Griffin *et al* 1994, Ninan *et al* 1995, Elder *et al* 1996), bronchial hyperreactivity (Frischer *et al* 1992) and lung function impairment (Coates *et al* 1977).

2.6.4 Infection

The role of respiratory infections in early life in the aetiology of asthma and allergic disease is complicated.

Infection with respiratory syncitial virus and rhinovirus are associated with the occurrence of bronchiolitis in early childhood. Infection with these viruses cause wheezing in young children due to airway hyperreactivity, inflammation and diminished lung function (Balfour-Lynn 1996). Martinez *et al*

(1995) have reported that about 30% of children aged less than three years have wheezing lower respiratory tract viral infections and that one third of these children still have wheeze at age six. Such infections are associated with smaller airways which are related to male gender, maternal smoking and pre-term birth. As the lungs grow and develop remission from bronchiolitis and wheezing illness may occur (Landau 1994). Many studies have shown that respiratory infections early in life are associated with the development of asthma later in childhood (Voter *et al* 1988, Busse 1990, Peat *et al* 1992a). Children with bronchiolitis during infancy are more likely to have non-specific BHR than children without such a history (Murray *et al* 1992). Further to this it has been reported that in later childhood up to 50% of asthma exacerbations are triggered by viral infections (Pattermore *et al* 1992).

Strachan (1989a) and von Mutius *et al* (1994) reported that factors directly or indirectly associated with smaller family size are related to a higher prevalence of hayfever and atopy in British and German children. There was also a suggestion that the first born child may be at higher risk. Shaheen *et al* (1996) reported that the prevalence of atopy was lower in young adults in Guinea-Bissau who had been infected with measles (which is associated with secondary bacterial lung infections) in early childhood. A possible explanation for this observation lies in the immune response to infection: There are two mutually exclusive patterns of cytokine release by different types of T helper cells. Early infections may cause a TH1- type response, with the production of γ-interferon. This cytokine can alter T cell differentiation and may down regulate the TH2 response which is associated with IgE production and allergic disease (Romagnani 1992).

It may be that early bacterial infections, which may be localised, protect against the development of atopy. Whereas, viral infections which may cause generalised inflammation, and perhaps facilitate the passage of allergens across the airway epithelium, may provoke an early manifestation of allergic

disease. Thus, reduced family size, fewer bacterial infections (or rapid antibiotic treatment of these infections) and possibly a higher incidence of viral infections in 'Western' areas may be a factors which partly explain the observed increase in asthma and atopy in recent decades.

2.6.5 Nutrition

2.6.5.1 Antioxidants

A free radical is defined as a molecule or atom that contains one or more unpaired electrons and is capable of independent existence (Halliwell and Chinico 1993). Free radicals are unstable, due to their unpaired electrons, and will react with any molecules or atoms in their vicinity. When a free radical collides with a non-radical the latter is converted into a radical, and a chain reaction of free radical formation is established which leads to cell and tissue damage (Halliwell 1991). Reactive oxygen species (ROS) include radicals that are derived from oxygen and molecules which are involved in the formation of radicals. ROS are the most important free radicals in biological systems, playing an important role in many metabolic processes including the inflammatory response, prostaglandin metabolism and cell death. When ROS formation exceeds elimination, equilibrium is upset and accumulation of ROS causes cell and tissue damage as DNA, lipids, proteins and carbohydrates are attacked.

A variety of enzymes are involved in the prevention of excess ROS formation, such as superoxide dismutase and glutathione peroxidase. Non-enzymatic chain breaking antioxidants include vitamins A (retinol), C (ascorbate) and E (α-tocopherol). Vitamin C scavenges ROS in plasma before they reach cell membranes (Nikki 1991): it is regenerated by the glutathione recycling system (Stadtman 1991). Vitamin A can prevent ROS formation and scavenges some free radicals, it accumulates in the cell membranes of some tissues and high concentrations are crucial for its effectiveness (Repine and

Heffner 1997). Vitamin E is a powerful antioxidant in plasma and cell membranes where it represents the principal defence against oxidant induced injury (Burton and Ingold 1989, Heffner and Repine 1989). The biological activity of vitamin E is dependent on dietary intake and the availability of vitamin C which maintains vitamin E in its reduced form (Packer 1979). Vitamin E is present in epithelial lining fluid (Heffner and Repine 1989).

Tissue damage in asthma is due to the production of ROS during the inflammatory process (Barnes 1990). In addition the lungs are vulnerable to attack from exogenous ROS in cigarette smoke and other air pollutants, and this requires that lung cells have a myriad of antioxidant strategies (Repine and Heffner 1997).

Several studies on antioxidants in adult respiratory disease support the role of antioxidants as protectants against lung injury. Dietary intakes and serum levels of vitamins A and C have been linked with reduced respiratory symptoms, improved lung function and reduced onset of obstructive pulmonary disease (Morabia *et al* 1989, 1990, Schwartz and Weiss 1990, Strachan *et al* 1991, Miedena *et al* 1993, Britton *et al* 1995, Troisi *et al* 1995). Soutar and colleagues (1997) showed reduced intake of vitamin C and the enzyme co-factors manganese and magnesium in adults with BHR. Selenium which is an important cofactor for red cell glutathione peroxidase activity has been shown to be reduced in asthmatics in New Zealand (Stone *et al* 1989, Flatt *et al* 1990).

Not all children with a genetic predisposition develop clinically significant disease; host antioxidant status could modify symptom severity (Burney 1995). Powell *et al* (1994) in a small cross-sectional study in Sheffield did not show any difference in serum antioxidant vitamin status between asthmatic children and symptom free controls. There are no data available on respiratory symptom severity and antioxidant status in children.

2.6.5.2 Fatty acids

The hypothesis that omega-3 fatty acids (which are found in large quantities in fish oils and butter) could ameliorate asthma symptoms is based on their potential to change inflammatory mediator action (Fisher and Weber 1994, Lee and Arn 1986). Lipid derived mediators such as leukotrienes and prostaglandins (eicosenoids) have a putative role in airway inflammation and asthma (Lewis and Austin 1984). Omega-6 fatty acids are the major precursor of eicosenoids in individuals consuming a usual Western diet; these fatty acids come from meat or from seed oils such as sunflower (Willis 1981). When diet is supplemented with fish oil, omega-6 fatty acids are substituted by omega-3 fatty acids in cell membranes. The resultant inflammatory mediators have different composition and less biological potency, thus decreased inflammatory activity (Thomgren and Gustafson 1981).

Studies on the beneficial effects of fish oils on asthma and other respiratory diseases have been inconclusive. Two studies by Arm and colleagues (1988, 1989) did not show any clinically significant improvement in asthma severity. Picado *et al* (1988) showed a reduction in expiratory flow and increased inhaler usage in aspirin-sensitive asthmatics on a fish oil supplemented diet. A prospective study found no protective effect of fish intake against the incidence of chronic non-specific lung disease (Miedena *et al* 1993). More recently cross-sectional studies by Schwartz and Weiss (1994), Sharp *et al* (1994) and Britton (1995) have shown beneficial effects of fish intake on lung function, particularly in smokers. A study from Australia showed reduced risk of asthma in children who consumed oily fish regularly (Hodge *et al* 1996).

2.6.5.3 Electrolytes

The proposed biological mechanism is that high sodium intake may lead to an increased contribution of the sodium pump mechanism to the cell

membrane resting potential which may potentiate hyperpolarisation of bronchial smooth muscle cells (Burney 1987). Animal models have shown that bronchial hyperreactivity is linked to increased sodium and potassium ion ATPase activity (Nath *et al* 1983, Souhrada and Souhrada 1983) and higher extracelluar potassium ion concentrations are related to increased smooth muscle contractility (Kakuta *et al* 1988, Black 1995). Further to this potassium homeostasis is regulated by the adrenergic system which is impaired in asthmatic subjects (Clausen 1983, Haas *et al* 1988).

Dietary intake of sodium has been reported to be associated with airway response to histamine (Burney *et al*, 1986) and regional asthma mortality rates in men and children have been linked to purchase of table salt (Burney 1987). A small study of disease severity in mildly asthmatic patients on diets with low, medium or high salt content showed no difference in PEF measurement or amplitude in patients with low and high salt intake (Lieberman and Heimer 1992). Investigators in Northern England found a relationship between urinary sodium excretion and BHR in one of three groups of men and concluded that if there is a "salt effect" that it is not likely to be strong (Deveraeux *et al* 1995). Demissie *et al* (1996) found no relationship between asthma or exercise induced bronchoconstriction and dietary salt, assessed by food frequency intake, although a relationship between bronchial hyperresponsiveness after methacholine challenge appeared to increase with greater salt intake in children. In contrast Sparrow *et al* (1991), Beack *et al* (1992) and Cerveri *et al* (1993) found no association between asthma and sodium intake. Britton and colleagues (1994a) did not find high dietary salt to be a risk factor for BHR after methacholine challenge or atopy assessed by skin testing.

The magnesium content of food is reduced during cooking and food processing, therefore a diet which includes a large component of refined foods is likely to be low in magnesium. Magnesium has a role in maintaining

cellular electrical potential and has been shown to relax airway smooth muscle (Skobelloff *et al* 1989). Britton *et al* (1994b) tested the hypothesis that low magnesium intakes could be related to respiratory morbidity. They reported that magnesium has an independent beneficial effect on lung function, BHR and wheezing in the general population.

It appears that low socio-economic status is associated with increased morbidity and a higher prevalence of asthma and wheezing illness in children (Mitchell *et al* 1989, Pattermore *et al* 1989, Shwartz *et al* 1990, Halfon Newacheck 1993). It may be that high salt intake, unhealthy diets and lifestyles are markers of socio-economic status rather than causally related to asthma (Demisse and Ernst 1994). Several of these factors are inter-related. For example smokers, who have a higher prevalence in low socio-economic groups, have been shown to have higher sodium intake and a less healthy diet compared to non-smokers (Fehily *et al* 1984, Fulton *et al* 1988, Margetts and Jackson 1993). Crawley and White (1996) also reported that adolescents with parents who smoke consume less vitamin C, vitamin E, folate, magnesium and fibre, as they had lower intakes of fruit juice, wholemeal bread and vegetables.

2.6.6 Summary

1. Asthma and atopy have a genetic basis which may determine host susceptibility to disease. This genetic component may be modified by a number of endogenous and exogenous factors.
2. Babies who are born with low birth weights and/or are premature are at increased risk of respiratory symptoms later in childhood. This effect is compounded if the mother is asthmatic and/or smokes during pregnancy.
3. Early bacterial infections may protect against the development of atopy, whereas viral infections may provoke early manifestations of

asthma. Reduced family size and fewer bacterial infections in 'western' areas may be a contributory factor related to the increase in asthma prevalence in recent decades.

4. Changes in dietary intakes over the last 30 years have been implicated as a contributory factor in the increased prevalence of asthma. There has been an increased consumption of processed foods, omega-6 fatty acids and salt, and reduced consumption of fresh produce (with higher 'natural' antioxidant content) and omega-3 fatty acids. It is proposed that such dietary changes have altered the host response to endogenous and exogenous oxidising agents.

5. Most published studies which have shown weak beneficial effects of improved host nutritional status on respiratory disease have been in adults. Stronger associations may be observed in children.

2.7 METHODS OF INVESTIGATION

2.7.1 Study design

Laboratory and chamber studies

These allow the effects of sole pollutants, combinations of pollutants or with allergens, and the effects of temperature, humidity and exercise to be studied under strictly controlled conditions. The main limitations are that only relatively short-term effects can be studied, and available subjects are usually healthy adults as severe asthmatics and children may be at increased risk from the effects of pollutants.

Panel and event studies

Panel studies recruit participants prospectively, subjects record lung function and symptom scores, each individual acts as their own control. These studies usually last for at least one month. Pollution levels are recorded at the same time, symptom scores and lung function are analysed according to pollution levels. Recruitment for event studies can be either prospective, in anticipation of a pollution episode, or retrospective when a pollution event has occurred and patients have symptoms and lung function already recorded.

Population studies

Population studies are performed in order to determine the occurrence of disease or symptoms. Cross-sectional studies are used to determine the prevalence (point, period or cumulative) of symptoms and diseases in different populations which can be compared. Risk factors associated with disease can be determined using a case-control study design. Cohort studies can be performed prospectively to study the natural history of disease.

2.7.2 Questionnaires

For studies to be comparable the same questions must be used, as the phrasing of a question can influence the response given. This has implications for translation of questions when comparative studies are performed overseas. Questionnaire responses are subjective and are influenced by a wide range of cultural, psychological and socio-economic factors (Toelle *et al* 1992). Questionnaire data are also prone to recall bias. Good return rates of questionnaires can reduce bias due to reporting by selected parts of the community. The use of schools to distribute and collect questionnaires has been shown to yield good returns compared to postal surveys (Powell and Primhak 1996). Brunekreef *et al* (1992) and Peat *et al* (1992b) have reported that questions to parents about diagnosed asthma, wheeze and dyspnoea in

children had good reproducibility, questions about period prevalence of cough were more reproducible than those about nocturnal and chronic cough. The International Study of Asthma and Allergies in Childhood (ISAAC) was developed to provide a standardised approach to international and regional comparisons of asthma prevalence and severity (Asher *et al* 1995). Part of the protocol involves the administration of a questionnaire, this method has been widely used and is accepted as a valid tool for the assessment of asthma prevalence in children (Pearce *et al* 1993, Busquets *et al* 1996, Jenkins *et al* 1996, Ponsonby *et al* 1996). Leung *et al* (1997) in a survey of 13-14 year olds using the ISAAC protocol reported 80% concordance between self administered written and video questionnaires. A higher prevalence of self reported wheeze was reported when the video questionnaire was used compared to the written format (Pearce *et al* 1993).

Seidman *et al* (1987) showed that recalled birth weight was accurate to within 100g and gestational age to within one week compared to hospital records in three-quarters of women. Another study showed that ten years after delivery 95% of mothers recalled birth weight correctly from broad categories (Tilley *et al* 1985).

2.7.3 Nutritional assessment

Dietary

Accurate measures of habitual food intake are important when assessing potential diet related risk factors or the protective effects of nutrients against disease. The method of dietary assessment has to be both accurate and feasible. There are several methods of assessing food intake: weighed records, food frequency questionnaire, 24 hour recall and estimated dietary diaries. Bingham *et al* (1994) showed that of the methods used for dietary intake assessment, the seven day estimated intake diary developed by

Bradden and colleagues (1988) was the most closely correlated with weighed food intake records.

Biochemical

Serum levels of vitamins A and E reflect the biochemical nutrient status of the host for these vitamins. Vitamin E circulates predominantly in the low density lipoprotein fraction of the blood. As serum lipid levels increase vitamin E, sequestered in membrane structures, partitions out of membranes into the circulating lipoprotein fraction (Blen *et al* 1977). Therefore it is important to use a vitamin E- lipid ratio otherwise vitamin E deficiency may be overlooked (Sokol *et al* 1985, Thurnham *et al* 1986).

2.7.4 Bronchial responsiveness

Bronchial reactivity is an essential element of homeostasis in healthy individuals, when reactivity is excessive it is termed bronchial hyperreactivity (BHR), This pathogenesis occurs in a significant proportion of asthmatics (McFadden 1997). BHR represents a spectrum of responses with arbitrary criteria, it has been reported that 20-30% of the non-atopic adults have BHR to inhaled methacholine (Casale *et al* 1987, 1988). Salome *et al* (1987) showed that 27% of symptomatic children did not have BHR. Analyses of available data by Cockcroft *et al* (1983) suggested that the distribution of BHR in the general population is unimodal, with asthmatics occupying the most highly sensitive end.

Direct and indirect methods

Tests of bronchial reactivity have a common basis: to provide a stimulus to the airways and record the change in lung function that develops. Pharmacological agents in aerosol form, such as histamine and methacholine, are used in direct bronchial responsiveness (BR) challenge tests. The

bronchoconstrictor effect is elicited by direct action of these agents on receptor sites in airway smooth muscle. Josephs *et al* (1990) demonstrated that methacholine and histamine challenges were vulnerable to variability within individuals. Dirksen and colleagues (1992) suggested that such variability was not related to variations in lung function, but that it is due to a factor associated with the pathogenesis of asthma.

Indirect challenge methods include exercise, osmotic (hypertonic saline) and isocapnic ventilation. The proposed mechanism of exercise induced bronchoconstriction (EIB) is that increased ventilation leads to airway cooling and water loss by evaporation which causes an increase in the osmotic pressure of epithelial lining fluid. It is proposed that the resulting bronchial responsiveness is mediated by interactions with inflammatory cells such as mast cells and neural responses (Pauwells *et al* 1980, Joos *et al* 1988, Haby *et al* 1994). Exercise tests have been shown to differentiate asthmatic children from those with other respiratory disorders (Godfrey *et al* 1991). Pattermore and colleagues (1990) have suggested that BR tests are not reliable or precise enough to separate asthmatics and non-asthmatics in the general community. Pharmacological and exercise challenges have been shown to identify different individuals, it has been suggested that different provocation tests identify different airway disorders (Bhagat and Grunstein 1984, Clough *et al* 1991, Haby *et al* 1994). In contrast, Wilson *et al* (1995) reported that there was no difference in five to six year old children in response to direct and indirect methods.

Both endogenous and exogenous factors have been shown to affect BR. Sears *et al* (1991) and Peat *et al* (1992a) have shown that atopy and increased BR are strongly related, Sears and colleagues (1993a) went on to show that the correlation between lung function and atopy was due to the association between BR and atopy. The link between viral infections is less clear and epidemiological studies have failed to show associations between

recent viral infection and increased bronchial responsiveness (Chan *et al* 1989a). Boulet *et al* (1983) showed increased bronchial responsiveness to exercise in non-asthmatics who were sensitised to grass pollen. Ozone and Nitrogen dioxide have also been shown to increase bronchial responsiveness (Orehek *et al* 1976, Holtzman *et al* 1979). Parental cigarette smoking has been shown to increase bronchial responsiveness in asthmatic and non-asthmatic children independently of the presence of atopy (Martinez *et al* 1988). Peat and colleagues (1990) showed prolonged bronchial responsiveness in asthmatic and non-asthmatic children after a cigarette smoke challenge. Platts-Mills and colleagues (1982) showed that bronchial responsiveness decreases after prolonged avoidance of known triggers.

Use of exercise challenge in population studies

Laboratory based protocols for exercise testing are performed by free or treadmill running or bicycle ergometer, although free running has been shown to be the most provocative form of exercise (Anderson *et al* 1971, Fitch and Morton 1971). The exercise period should be six to ten minutes in duration and at a level of 75% maximum predicted heart rate. The degree of bronchoconstriction induced depends on the temperature and humidity of the inspired air. The stimulus can be increased by inspiring cold, dry air, thus ideally the temperature and humidity of the air should be controlled (McFadden 1987). Maximum constriction occurs five minutes after the exercise period therefore serial measurements of lung function should be recorded. Silverman and Anderson (1972a) and Tsanakans *et al* (1988) have developed standard free running exercise protocols.

Pattermore and Holgate (1993) showed that for a single BR challenge test the positive predictive value (the likelihood of a child with a positive test result having asthma) and the negative predictive value (the likelihood of a child with a negative test result not having asthma) to be poor, due to a

proportion of non-asthmatic children having a positive test result and a greater proportion of asthmatic children having a negative test result. Though such discrepancies between a single challenge test result and a history of respiratory symptoms may be explained by the variable nature of the asthmatic condition. Pattermore *et al* (1990) in a study of New Zealand schoolchildren showed that 42% of children with wheeze in the previous 12 months had negative test results and 41% of children with BR to histamine had no asthma symptoms. The resulting fall from baseline in FEV_1 used to define EIB varies between 10 and 20%. If this threshold were increased to 25% the specificity of the test would be increased but the sensitivity would be reduced.

The use of exercise testing for screening populations for asthma has been shown to be successful (Williams *et al* 1993), although it has been suggested that its use may be no more sensitive than a symptom questionnaire (Ninan and Russell 1993). Powell *et al* (1996b) reported that exercise tests had poor reproducibility and significant within individual variability. Further to this Hill and colleagues (1991) demonstrated that the use of exercise tests in screening for asthma and referring children with positive tests to their GP did not reduce respiratory morbidity.

2.7.5 Hypersensitivity

Skin-prick testing can be performed in epidemiological studies to determine whether or not an individual is atopic. The principle is that the 'weal and flare' reaction which occurs when an allergen is introduced to the skin indicates the presence of mast cell fixed antibody, particularly IgE (Dreborg 1989). The definition of a positive skin test is based on the diameter of the weal, arbitrary cut-off points of between one and three millimetres more than the saline control indicate positivity. The potency of the allergen extract is related to the size of the weal, thus problems arise when comparing studies

which have used allergen extracts from different manufacturers. Positive skin tests have been shown in individuals with no evidence of allergy (Curran and Goldman 1961, Fontana *et al* 1963, Lessof *et al* 1980, Bousquet 1988). Negative results to common aeroallergens such as house dust mite, cat, dog, pollens and moulds occur in patients with well characterised allergies. Pepys (1975) observed that 17% of asthmatics sensitive to grass pollen had negative skin tests to grass pollen.

2.7.6 Summary

1. The use of standardised questions is required for direct comparison of surveys between different populations.
2. Estimates of asthma prevalence differ depending on the definition used; questionnaire reported symptoms and asthma diagnosis by doctors show different results to prevalence estimates based on positive bronchial provocation tests.
3. BHR testing over short time periods may yield variable results which may be due to individual variation in bronchial responsiveness. Direct and indirect provocation tests may identify different airway disorders.
4. Estimated dietary intake records are an accepted and reasonably reliable method for estimating nutrient consumption.

Chapter Three

Methods for cross-sectional surveys and longitudinal survey

3.1 Background

The recent history of coal importation at the Bootle Docks in North Liverpool and community concern about the possible effects of dust on the respiratory health of children were described in section 1.1.

3.2 Study design

Cross-sectional

In 1991 a cross-sectional survey of respiratory health in primary school children (aged 5-11 years) was performed to determine the prevalence of respiratory symptoms and asthma in the area close to the Bootle Docks compared to two other areas in Merseyside with similar socio-economic status. All three areas were recognised to have major unemployment and housing problems, and it was thought before the study that these were of similar magnitude.

A second cross-sectional survey of respiratory health was performed in 1993 in the same primary schools. This was undertaken in order to ascertain whether there was any change in the prevalence of respiratory symptoms associated with expected reductions in dust levels due to improved coal handling procedures.

Longitudinal

A cohort of children who were surveyed in 1991 who were still attending the same school at the time of the 1993 survey were identified. This group of children were re-surveyed in order to estimate rates for recovery and incidence of respiratory symptoms.

3.3 Definition and location of study groups

Figure 3.1 shows the locations of the 15 primary schools which took part in the respiratory health surveys. Figure 3.3 shows the coal stockpiles in

1991. Figure 3.5 shows the proposed new handling facility at the North Bootle Dock.

Coal dust exposed group (exposed)

This group consisted of children residing and attending the five primary schools in geographical proximity to the coal handling terminal, including the area from which the nuisance complaints had occurred. One of the housing estates and a primary school were situated within 200 metres of where the coal was stockpiled (figure 3.2). The other schools were located between one half to two kilometres from the coal handling terminal.

Control group 1 (non-exposed)

Children attending five primary schools five kilometres Southwest of the coal stockpiles, and thus upwind of the prevailing winds. This is a dockland area on the Wirral side of the River Mersey, where the docks are largely non-operational (figure 3.4). Socioeconomic status was considered to be comparable to that in the exposed area.

Control group 2 (non-exposed)

Children attending five primary schools three to eight kilometres North and East of the coal terminal. There were no complaints of coal dust nuisance from residents in this area. Socioeconomic status was considered to be comparable to the exposed area.

3.4 Questionnaire

The questionnaire was a modified version of that designed and used by Clifford *et al* (1989) which had been shown to have good return rates. In their survey a subset of parents had been re-surveyed four months after the

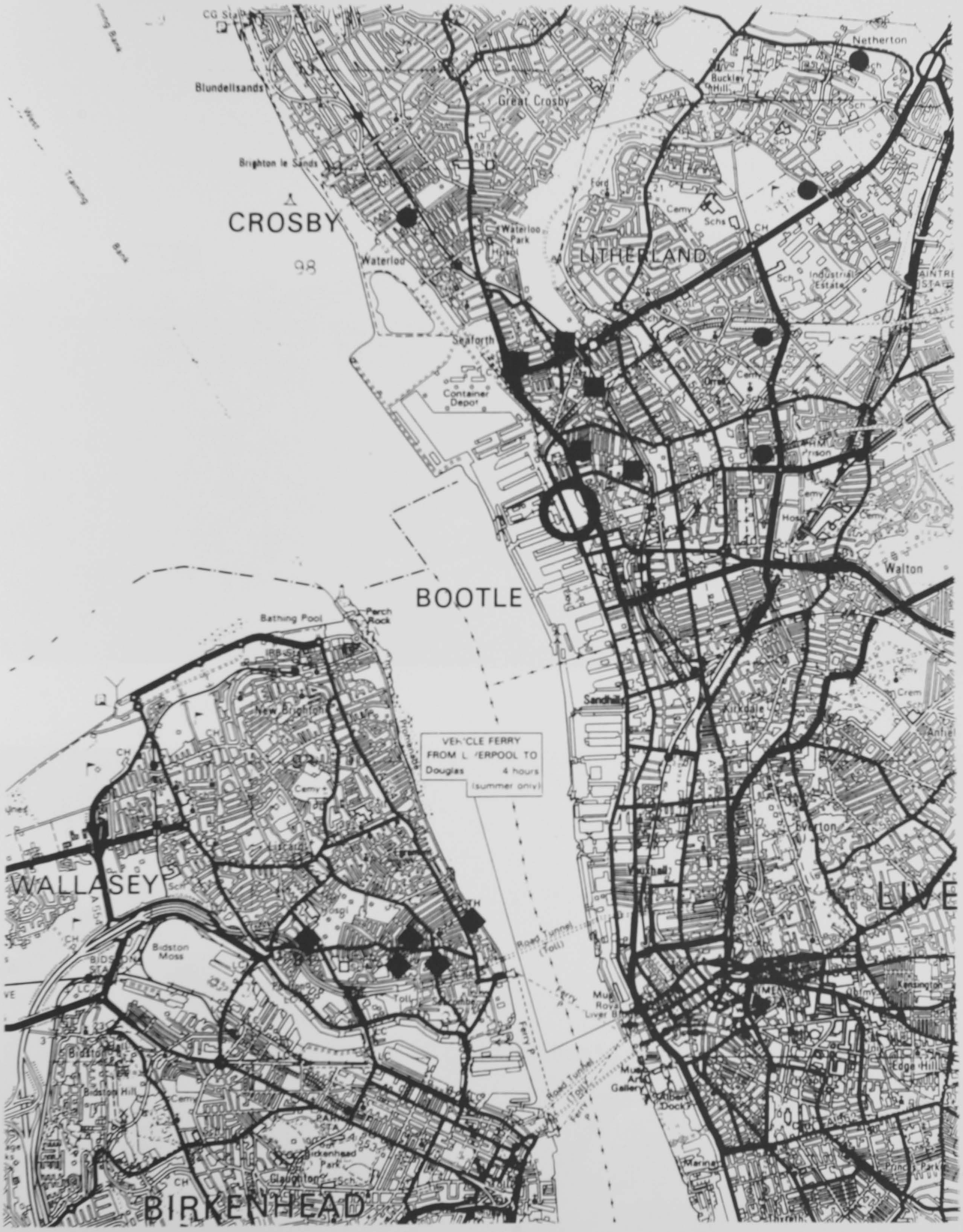
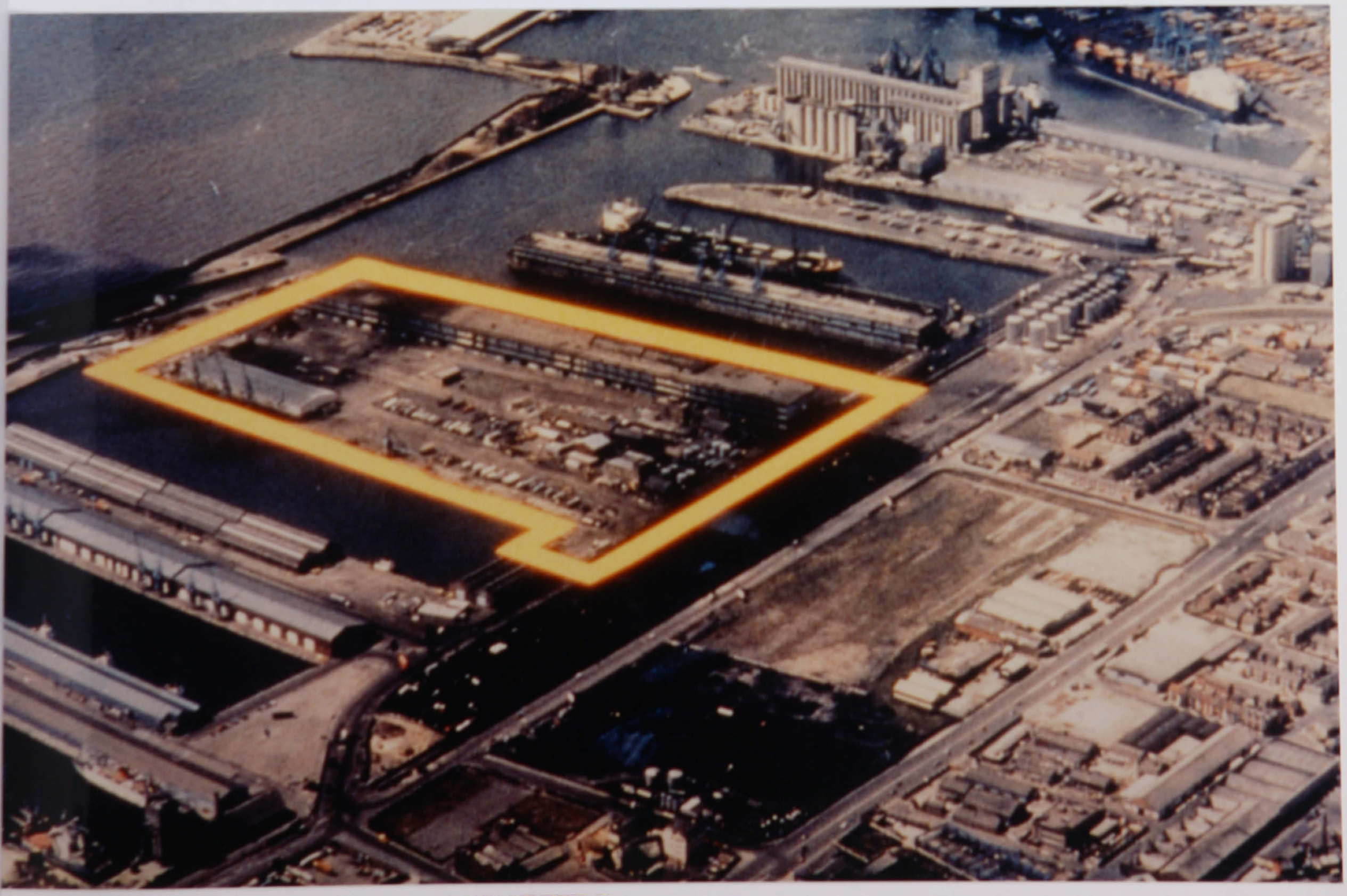


Figure 3.1 Map of the three study areas, the large open circle rings the area of the coal stockpiles.

■ *-Exposed area* ◆ *-Control area 1* ● *-Control area 2*


S 11'80
Q 12'6



initial survey and questions about cough, wheeze, breathlessness, absence from school due to respiratory symptoms and hospital admissions were shown to be reproducible. The questionnaire was initially piloted with 20 parents in order to make it user friendly and the format appropriate for self-completion. The opinions of headteachers were also sought on questionnaire design. The presence of cough, wheeze and breathlessness was determined by the questions; 'Has your child ever had an attack of wheezing (by wheezing I mean noisy breathing and a whistling sound coming from the chest) ?'; 'Has your child ever been unexpectedly breathless at rest or more breathless than expected after exercise (by breathless I mean out of breath or puffed) ?'; 'Has your child ever seemed to cough more (or get more coughs) than other children ?' Questions on demographic and socio-economic factors were also asked in order that risk factors for respiratory morbidity other than dust pollution could be assessed. Questions included those about employment status of parents, presence of smokers in the household, dampness in the home, pet ownership, heating, parental asthma and current prescribed medication usage. Parents were asked to record the child's birthweight, prematurity was assessed by the question 'Was your baby born prematurely', infant feeding practices were also ascertained, (Appendix A for full questionnaire). In 1993 additional questions were asked about parental smoking habits during pregnancy, (Appendix B). See appendix C for parent information document which accompanied the questionnaire.

3.5 Air pollution

The municipal Public Protection Departments of Sefton and Wirral were monitoring dust level measurements by using British Standard Deposit gauges (BS1747 1969) as part of an environmental assessment of these areas throughout the periods of study. These measurements were undertaken by chemists working for the Public Protection Department and dust levels

were made available for analysis. Four-weekly measurements were first obtained in December 1990 and regular monitoring has continued since that time. Monitoring gauges were placed at fixed sites on lamp posts and school roofs. Samples were obtained from one gauge in each study area. Measurements were of total undisolved solids, expressed as $mg/m^2/day$.

3.6 Sample size

In order to estimate a difference in the prevalence of respiratory symptoms due to an environmental factor between two groups (exposed *vs* control 1, exposed *vs* control 2 or control 1 *vs* control 2) where no estimate of exposure was available, an estimate of symptom prevalence of 10% and relative risk of 1.5 with 90% power required 525 children in each group. Five schools in each area were chosen for study. In 1991 there were 4084 children in the 15 primary schools, a return rate of completed questionnaires of 75% was assumed, thus questionnaires were distributed to every second child on the alphabetically ordered school registers (n=2035). In 1993 there were 4288 children in the same 15 schools including a cohort of children who were seen in the 1991 survey and were identified from school registers. Every child in each school was surveyed, which resulted in 1202 in the follow-up cohort and 3086 in the cross-sectional survey.

3.7 Study implementation

Questionnaires were delivered to schools and distributed to parents via class teachers, parent completed questionnaires were returned to the schools and collected during a school visit by a research worker. Informed written consent was obtained from parents to measure height, weight and peak expiratory flow (PEF) in all children in the 1991 survey. In 1993 these measurements were taken for those children in the longitudinal cohort only. Children were asked to remove their shoes, socks and heavy garments,

height was measured to the nearest millimetre using a Minimere, weight was measured to the nearest 100 grams using electronic scales. Children were instructed how to perform a forced expiratory manoeuvre and after sufficient practice the highest of three PEF readings was recorded. A mini-Wright peakflow meter was used for all readings. Nose-clips were not worn. Schools were re-visited one week after the initial visit to survey absentee school children.

In 1991 and 1993 children were surveyed between October and December with surveys running concurrently in all three areas.

Ethical permission was obtained from the District Health Authority and the Local Education Authority for each area.

3.8 Statistical analyses

Statistical analyses were performed using Epi Info and the Statistical Package for Social Sciences (SPSS). Univariate stratified analyses of cross-sectional data were performed, chi-square and significance values were calculated at the 5% level using contingency tables for categorical variables. Univariate analysis was performed to determine between survey changes in socio-economic and respiratory factors. Analysis of variance was applied to continuous data. Multiple logistic regression analyses were performed to assess risk factors for respiratory symptoms. The McNemear test was applied to data for the longitudinal cohort to assess short-term temporal changes.

Chapter Four

Respiratory health of children in an area of dust and air pollution

4.1 Introduction and objective

Air pollution with substances known to be allergenic has been shown to cause asthma (Anto *et al* 1989). It is not clear whether substances not known to be allergenic or directly irritant to the airways can lead to increased bronchial hyperreactivity. Neither is it known whether such effects would apply to everyone or just specific groups in the population, such as children with an atopic diathesis (Andrae *et al* 1988, Finn 1992). The objective of this chapter was to determine whether there was increased respiratory morbidity in primary school children living and attending school in an area of Merseyside with known increased levels of airborne dust pollution compared to children living and attending school in control areas with lower levels of airborne dust pollution.

4.2 Methods

In 1991 a parent completed questionnaire (Appendix A) was distributed through 15 primary schools to every second child on the school register (n=2035). Questions were asked about the respiratory health of the parents and the study child, home environment and socio-economic factors. Children attended five schools in each of the three areas defined in chapter three, i.e. the exposed area and two control areas. During a school visit height, weight and PEF were measured. Re-visits were made for absentees. Air pollution measurements from British Standard Deposit Gauges were made available by the Public Protection Department.

Univariate stratified analyses were used to compare socio-economic and respiratory health data for children in the dust exposed area compared to the two control areas. Multiple logistic regression was used in order to estimate the magnitude of the risks associated with different factors for the respiratory outcome variables, wheeze, diagnosed asthma and school absence due to respiratory symptoms.

4.3 Results

STUDY POPULATION

92% (1872/2035) of the questionnaires were returned. Of these 78.5% were completed by the mother, 4.8% by the father and 15.8% by both parents. The response rates in the three areas were similar. Compliance in the schools from which much of the initial concern about dust pollution and asthma had originated was comparable with other schools (92% and 99%). Some of the questionnaires were not fully completed, though the proportion of responders who completed the questions relating to asthma diagnosis, cough, wheeze and breathlessness did not differ between the areas.

There were significant socio-economic differences between the exposed and control areas. Parental unemployment, rented accommodation, damp housing and the presence of smokers in the household were more common in the exposed compared to control areas (table 4.1). Mean age, height and PEF were significantly lower in control area 1 compared to control area 2 and the exposed area. Children from the exposed area had lower mean birthweights and were not breastfed as often nor for as long as children in control areas (table 4.2). There were no significant socio-economic differences between the two control areas and so these data were pooled for subsequent analyses.

UNIVARIATE ANALYSIS

The prevalence of doctor diagnosed asthma, wheezing, breathlessness, excess cough and absences from school due to respiratory symptoms were higher in the exposed compared to control areas (table 4.3). There were no differences in other factors between the groups associated with asthma, such as parental asthma and a history of allergies. There was no difference in the prevalence of eczema, hayfever or croup, nor the duration of wheeze or attacks of breathlessness or their age of onset between the three

Table 4.1 Prevalence of socio-economic variables in control and exposed groups. Values are % (number)

Variable	*Control area 1*	*Control area 2*	*Exposed area*	*Significance (p value)*	
				Exposed vs control area 1	*Exposed vs control area 2*
Maternal employment	46.6 (646)	42.5 (633)	27.4 (121)	<0.001	<0.001
Paternal employment	71.1 (564)	71.0 (558)	59.5 (363)	<0.001	<0.001
Rented home	34.2 (669)	44.9 (648)	64.5 (462)	<0.001	<0.001
Damp house	15.6 (652)	11.8 (645)	21.4 (448)	<0.25	<0.001
Smokers in house	58.6 (679)	60.3 (675)	70.6 (476)	<0.001	<0.001
Pet in house	63.2 (688)	50.1 (659)	54.4 (471)	<0.01	NS

NS = not significant at the 5% level.

Table 4.2 Demographic and birth factors for control and exposed areas. Values are mean (SD) for continuous variables and % (number) for categorical variables

				Significance (p value)	
Variable	*Control area 1*	*Control area 2*	*Exposed area*	*Exposed vs control area 1*	*Exposed vs control area 2*
Age, yrs	7.4 (2.0)	7.7 (2.0)	7.7 (2.0)	<0.01	NS
% Sex, male	51.3 (680)	48.8 (687)	53.7 (482)	NS	NS
Height, m	1.23 (0.12)	1.25 (0.12)	1.25 (0.13)	<0.05	NS
Weight, kg	25.6 (7.6)	26.6 (7.5)	26.3 (7.2)	NS	NS
Peakflow, l/min	226 (71.7)	238 (69.1)	242 (68.6)	<0.001	NS
Birthweight, kg	3.29 (0.56)	3.30 (0.60)	3.24 (0.57)	NS	NS
Pre-term birth	15.4 (676)	13.2 (667)	15.2 (475)	NS	NS
Breast fed	36.0 (678)	34.8 (672)	25.3 (474)	<0.001	<0.001
Duration of feeding, months	4.5 (4.5)	4.6 (4.5)	4.0 (3.4)	NS	NS

NS = not significant at the 5% level

Table 4.3 ***Respiratory variables*** *in control and exposed groups. Values are % (number)*

Variable	*Control area 1*	*Control area 2*	*Exposed area*	*Significance (p value)*	
				Exposed vs control area 1	*Exposed vs control area 2*
Ever diagnosed asthma	17.0 (675)	15.3 (675)	21.1 (474)	NS	<0.025
Ever diagnosed bronchitis	11.0 (665)	9.5 (653)	16.5 (462)	<0.01	<0.001
Ever diagnosed croup	14.1 (665)	12.3 (653)	14.2 (458)	NS	NS
Well controlled asthma*	82.3 (124)	87.8 (115)	72.1 (111)	NS	<0.01
Maternal asthma	7.7 (660)	5.9 (641)	7.5 (452)	NS	NS
Paternal asthma	5.5 (633)	6.1 (642)	7.1 (439)	NS	NS
Attack of wheezing	20.6 (656)	17.5 (644)	25.0 (448)	NS	<0.01
Attack of breathlessness	11.2 (663)	10.2 (650)	19.1 (451)	<0.001	<0.001
Excess cough†	25.1 (686)	23.4 (670)	40.0 (480)	<0.001	<0.001
Ever admitted to hospital for respiratory symptoms	9.5 (664)	3.5 (651)	8.2 (408)	NS	<0.001
Absent from school for respiratory symptoms‡	11.7 (642)	11.9 (638)	21.2 (453)	<0.001	<0.001
Allergies, eczema, or hay fever	16.7 (610)	12.7 (612)	13.6 (427)	NS	NS
All drugs prescribed	13.8 (675)	10.7 (663)	17.7 (468)	NS	<0.001
Antiasthmatic drugs	9.9 (675)	6.2 (663)	11.7 (468)	NS	<0.001

NS = not significant at the 5% level.
* Proportion of those with asthma in whom it was well controlled.
† Child who seems to cough more (or get more coughs) than other children.
‡ Absent for six or more days in preceding 12 months.

Table 4.4 Compliance and respiratory indices (%) in individual schools

	Control area 1					Control area 2					Exposed area				
Variable	*1*	*2*	*3*	*4*	*5*	*1*	*2*	*3*	*4*	*5*	*1*	*2*˙	*3*	*4*˙	*5*
Compliance	86	95	98	89	76	93	93	96	79	76	92	99	84	99	82
Well controlled asthma†	96	86	75	83	65	97	84	92	70	82	80	62	86	75	58
Attack of wheezing	23	19	20	26	18	20	17	20	15	15	17	22	23	32	23
Attack of breathlessness	7	12	12	13	10	11	10	10	9	9	14	17	11	25	19
Excess cough‡	27	24	26	22	23	21	24	26	21	22	37	38	33	43	43

˙ The two schools closest to coal stockpile. Schools coded 1 and 2 in the exposed area were those from which the original complaints were received. † Proportion with well controlled asthma. ‡ Child who coughs more than other children.

Table 4.5 Prevalence (%) of diagnosed asthma and respiratory symptoms for both sexes

	Control area 1		Control area 2		Exposed area		Total	
Variable	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
Diagnosed asthma	18.5	15.6	18.2	12.5	26.4	13.1	20.6	14.3‴
Wheeze ever	22.2	19.0	20.4	14.7	28.8	20.8	23.3	17.8‴
Breathlessness ever	12.7	9.6	12.0	8.4	23.4	14.2	15.3	10.2‴
Cough ever	23.9	26.3	25.2	21.8	41.0	38.7	29.0	27.7

‴ $p<0.01$, ‴ $p<0.001$ comparing boys *vs* girls

areas. Within each area the reporting of excess cough, wheeze, breathlessness and control of asthma was comparable between schools (table 4.4). Diagnosed asthma and wheeze were less common in girls than boys in all areas, but there were no sex differences in the prevalence of cough (table 4.5).

The symptom triad of cough, wheeze and breathlessness was more common in the exposed area (12.7% vs 7.1% and 5.4%), as was the sole symptom of excess cough (13.6% vs 7.1% and 6.2%) compared to the control areas (table 4.6).

Table 4.6 Composite respiratory symptom prevalence (%) in study areas

Respiratory symptoms[•]	*Control area 1 (n=637)*	*Control area 2 (n=616)*	*Exposed area (n=426)*
C+ B+ W+	7.1	5.4	12.7[†]
C+ B- W-	7.1	6.2	13.6[†]
C+ B- W+	5.0	3.9	4.2
C+ B+ W-	1.1	1.1	3.0
C- B+ W+	1.3	1.5	1.6
C- B- W-	69.1	71.3	54.2[†]
C- B- W+	4.6	3.4	3.5
C- B+ W-	0.0	0.8	0.9

C = excess cough during last 12 months; B = severe attack of breathlessness at any time; W = attack of wheezing at any time. + or - indicates the symptom present or absent.
• Total do not make 100% as about 6% of children reported a cough but not in preceding 12 months.
† Exposed *vs* control 1 or 2, $p<0.01$.

High prevalence figures for respiratory indices were reported for children in the exposed area whose parents considered dust exposure to be associated with respiratory symptoms (lifetime diagnosis of asthma 42.2%, breathlessness 41.2%, excess cough 75.5%, hospital admissions due to respiratory symptoms 17.3%), but there was no difference in the mean PEF measurement of these children compared to children in the exposed area whose parents did not consider dust pollution to be a problem.

Table 4.7 shows the distribution of lost school days due to cough, wheezing or

breathlessness in the three areas. A significantly higher proportion of children in the exposed area lost time from school for six days or more in the preceding year due to respiratory symptoms compared to control groups.

Table 4.7 Distribution of school days lost in preceding 12 months due to respiratory symptoms. Values are %

School days lost	*Control area 1*	*Control area 2*	*Exposed area*
None	65.1	64.1	52.5
1 - 5	23.2	24.0	26.3
6 - 10	8.6	9.9	15.2
>20	3.1	2.0	6.0

Table 4.8 shows the prevalence of respiratory variables for each area, further stratified by passive smoke exposure. Croup, bronchitis, wheezing, breathlessness, excess cough, school absences and less well controlled asthma are more common in children from smoking environments.

AIR POLLUTION DATA

Air pollution data are incomplete due to vandalism of some of the sampling equipment. Dust pollution levels were significantly higher in the exposed area compared to control areas (table 4.9, see appendix D for more complete dust mesurements for exposed and control areas). A large proportion of insoluble matter in samples from the exposed area was combustible matter (exposed area 39.2%; control 1, 6.3%; control 2, 6.5%), which may consist of unburnt coal dust, partially combusted coal, oil or other organic matter. In the exposed area, for three of the sampling periods dust deposition rate exceeded 200 $mg/m^2/day$. It was not possible to further analyse samples due to the destructive nature of the initial test.

Table 4.8 Respiratory variables in control and exposed groups in relation to passive smoking. Values are % (number)

	Control area 1		Control area 2		Exposed area	
Variable	*Non-smoking*	*Smoking*	*Non-smoking*	*Smoking*	*Non-smoking*	*Smoking*
Ever diagnosed asthma	17.4 (276)	16.9 (396)	13.1 (267)	16.7 (406)	22.1 (140)	20.7 (334)
Ever diagnosed bronchitis	8.8 (274)	12.6 (389)	7.8 (256)	10.6 (396)	15.4 (136)	16.9 (326)
Ever diagnosed croup	11.6 (275)	15.7 (388)	10.2 (256)	13.6 (396)	12.7 (134)	14.8 (324)
Well controlled asthma*	88.2 (51)	78.1 (73)	94.3 (35)	85.0 (80)	83.9 (31)	67.5 (80)
Maternal asthma	7.7 (260)	4.1 (363)	4.8 (249)	6.8 (384)	6.9 (131)	7.3 (300)
Paternal asthma	6.0 (267)	8.6 (383)	3.9 (255)	6.6 (376)	8.3 (132)	7.3 (313)
Attack of wheezing	17.3 (271)	23.0 (374)	15.4 (253)	18.7 (380)	23.3 (129)	25.3 (312)
Attack of breathlessness	8.4 (273)	12.9 (379)	8.1 (259)	11.9 (380)	17.2 (128)	19.9 (317)
Excess cough†	20.1 (278)	28.6 (396)	20.0 (265)	25.1 (394)	36.3 (138)	41.6 (334)
Ever admitted to hospital for respiratory symptoms	7.8 (268)	10.7 (385)	3.1 (256)	3.6 (386)	9.0 (134)	8.0 (327)
School absent for respiratory symptoms in last year‡	30.8 (260)	37.7 (371)	30.5 (253)	38.8 (376)	46.0 (126)	48.0 (321)
Allergies	15.9 (258)	17.4 (350)	13.9 (244)	12.0 (367)	17.7 (130)	11.8 (297)
Drugs prescribed§	15.3 (281)	12.5 (392)	12.3 (261)	9.8 (400)	18.2 (137)	17.5 (331)

* Proportion of those with asthma in whom it is well controlled.
† Child who seems to cough more than other children.
‡ Absent for one or more days.
§ 70% of all drugs were for asthma.

Table 4.9 Summary of the British Standard dust deposit gauge results in exposed area (December 1990 to November 1991)

		Undissolved deposited matter ($mg/m^2/day$)			
Location	*No of samples*	*Mean (SD) annual amount*	*Median*	*Minimum*	*Maximum*
1	12	148.8 (50.5)	151.4	45.3	245.9
2	13	109.4 (45.8)	100.9	44.0	200.9

Based on four weekly sampling periods.

MULTIPLE LOGISTIC REGRESSION

Multiple logistic regression models were constructed for diagnosed asthma, wheezing and school absenteeism. Chi-square values and odds ratios were calculated for each potential risk factor and if the chi-square was significant at the 10% level ($p<0.1$) the variable was a candidate for inclusion in the model. Risk factors fell into several broad categories, includingallergies, family history of asthma, household pets, presence of smokers in the household. dampness, parental employment, sex, age and area (exposed or control).

Table 4.10 shows significant risk factors after adjustment for confounding factors. Risk factors for wheezing were allergies, parental asthma, male sex, passive smoke exposure and paternal unemployment. Allergies, parental asthma, male sex and rented accommodation were risk factors for diagnosed asthma. School absenteeism due to respiratory symptoms was associated with allergies, attending school in the exposed area, passive smoking, maternal unemployment and other health problems.

4.4 Discussion

QUESTIONNAIRE

A questionnaire similar to the one used had previously been validated in Southampton (Clifford *et al* 1989). The excellent response rate of more

than 90% was better than some recently reported studies of children; Birmingham 69% and 84% (Ayers *et al* 1992); Munich and Leipzig 76% and 88% (von Mutius *et al* 1992); Switzerland 74% (Braun-Fahrlander *et al* 1992); Monkton Coking Works Study 78% (Bhopal *et al* 1992). Questionnaires were distributed through schools, a method which has been reported to be associated with high compliance elsewhere (Powell and Primhak 1996a). The high response rate and comparability of responses between the schools increases confidence in the data.

Table 4.10 Adjusted odds ratio for risk indices from multiple logistic regression

Variable	*Odds ratio*	*95% Confidence interval*
Wheezing (n=1272)		
Any allergy	4.95	3.52 to 6.96
Either parent with asthma	2.41	1.60 to 3.62
Sex (girl)	0.66	0.49 to 0.89
Father unemployed	1.44	1.05 to 1.97
Passive smoking	1.44	1.05 to 1.98
School in exposed zone	1.37	0.98 to 1.91
School absenteeism* due to cough, wheezing, or breathlessness (n=1391)		
Any allergy	2.72	2.02 to 3.66
School in exposed zone	1.59	1.23 to 2.04
Passive smoking	1.33	1.05 to 1.68
Other health problems	1.36	1.05 to 1.75
Mother unemployed	1.29	1.02 to 1.63
Ever diagnosed asthma (n=1409)		
Any allergy	6.27	4.49 to 8.74
Mother has diagnosed asthma	2.68	1.38 to 5.20
Father has diagnosed asthma	1.97	1.09 to 3.55
Sex (girl)	0.70	0.52 to 0.95
Rented home	1.37	1.00 to 1.87
School in exposed area	1.25	0.88 to 1.76

*More than one day in preceding 12 months.

Children in the three study areas were studied in parallel over a three month period so that any climatic or seasonal influences would have had the same effect on each group.

RESPIRATORY FACTORS

The school closest to the coal terminal had been the subject of much press speculation. Questionnaire responses about respiratory indices did not differ between this school and the other four schools in the exposed area. The proprtions of responders who completed questions relating to respiratory factors was similar in control and exposed areas. Reporting of croup, hayfever and eczema were comparable in the three areas, therefore it seems reasonable to conclude that parents in the exposed area did not answer 'yes' indiscriminately to all questions. Thus over-reporting of symptoms by parents in this exposed area was not considered to be a major source of bias. The increased prevalence of cough and absences from school due to respiratory symptoms would seem to reflect genuine morbidity in the exposed area.

The prevalence of wheeze and cough in the control areas was comparable to that reported by Clifford *et al* (1989) and Ninan and Russel (1992). This suggests that in 1991 the prevalence of these symptoms in relatively non-polluted areas of Merseyside was similar to that elsewhere in the UK.

The exposed area was more deprived than either of the control areas, with higher levels of unemployment, parental smoking and rented accommodation. The higher prevalence of respiratory morbidity in the exposed area was evident from both univariate and multiple regression analyses. The latter method controlled for the effects of all known confounding factors, including socio-economic variables, however it is possible that an unidentified factor, such as standards of hygiene may be

exerting an effect. Nevertheless it is clear that there is an excess of respiratory morbidity in the exposed area.

Asthma and wheezing are recognised as causes of school absenteeism, and school days lost for this reason in the control areas were comparable to that reported in Nottingham (Hill *et al* 1989a).

Before the study the parents had labelled the respiratory problem as asthma. There was a higher prevalence of doctor diagnosed asthma in the exposed area, although the most striking statistical association was the occurrence of excess cough. Excess cough either as a solitary symptom or in combination with wheeze and breathlessness (a likely combination for childhood asthma, Kelly *et al* 1996/Chapter five) was markedly more common in the exposed area. If air pollution and respiratory symptoms are associated, these observations suggest that an increased dust burden may be linked to increased cough in exposed children.

Peak flow measurements were within the expected range (Godfrey *et al* 1970) The lower mean PEF measurement in control area 1, compared to control area 2 and the exposed area, can be explained by these children's lower mean age and height.

It is established that adults working in dusty jobs may develop productive cough, referred to as 'simple bronchitis', this occurs without airflow limitation (Morgan 1984). In general coal dust is not held to be the cause of airway obstruction in miners; this is a controversial area with the effect of cigarette smoking heavily confounding the effect of coal dust on miners' respiratory health. Occupational respiratory disease studies are however restricted to adults, and children's lungs may handle a dust burden differently. Moreover children living and attending school with an increased level of pollution are exposed 24 hours a day whereas occupational exposures last for fewer hours. Thus there are difficulties in comparing the effects of chronic

exposure in children to perhaps more acute exposure associated with occupation in adults.

Children exposed to passive smoke are more likely to have wheeze and time off school due to respiratory symptoms. The harmful effects of passive smoke exposure on childhood respiratory health have been widely accepted and well documented. Increased risk of respiratory infections and wheezing illnesses in children who are exposed to passive smoke compared to those who are not have been reported (Somerville *et al* 1988, Chinn and Rona 1991, Wright *et al* 1991, Braback *et al* 1995, Stoddard and Miller 1995, Strachan *et al* 1995).

AIRBORNE POLLUTION

The study design was cross-sectional and although it can be stated that there is a respiratory health problem in children in the exposed area, a specific cause cannot be attributed. The relatively recent dust problem in the dock area provides a straightforward explanation for the observed higher morbidity in the exposed area. In particular the occurrence of excess cough suggests that the problem is due to inhalation of dust. The World Health Organisation guidelines for particulates state that concentrations of respirable particles should not exceed 50$\mu g/m^3$/day (Holman 1994), whereas the average dust deposition rate in the exposed area was 146 mg/m^2/day and on three of the sampling occasions deposition exceeded 200mg/m^2/day. However, it is not clear what proportion of the dust collected in the sampling gauges was respirable (<10 μm in diameter). It is reasonable to assume that the contribution of pollutants from motor vehicle exhausts would be comparable in each of the study areas as they are all situated in the vicinity of major roads.

Other cargoes handled at the docks are a potential source for concern. The unloading of grain is mostly by enclosed procedures, however animal

feeds which are unloaded intermittently are not well handled and these could be a source of allergenic dusts which could provoke asthma. Analysis of the deposited particles showed that more than a third was carbonaceous in the exposed area compared to about six percent in the control area. Hospital admissions for asthma were not increased, thus it seems that there were no 'epidemic' episodes of asthma admissions which have been associated with allergenic dust exposures elsewhere (Anto *et al* 1989).

A study from South Wales reported an increase in asthma diagnoses by general practitioners when a new surface coal mine began operation, although it was not clear whether this was due to the overdiagnosis of cough (Temple and Sykes 1992). Braun-Fahrlander *et al* (1992) reported that respiratory symptoms were more common in Swiss children in an area with increased levels of total suspended particulates, these observations were independent of SO_2 and NO_2 levels. The Monkton Coking Works Study reported that respiratory symptoms were more prominent in children than adults (Bhopal *et al* 1992). Colley and Brasser (1989) showed that in eight European countries smoke and sulphur dioxide pollution was related to indices of respiratory disease in children, such as cough, dyspnoea and bronchitis. The occurrence of wheeze was not associated with either pollutant. Smoke appeared to have the greater effect on respiratory health. Von Mutius *et al* (1992) reported that there was an increased risk of bronchitis for children living in the former East German city of Leipzig, which had high levels of particles and SO_2, compared to children in Munich, with higher levels of NO_2 and O_3, where there was an increased risk of hayfever. Inverse relationships between PEF and PM_{10} levels have been reported in asthmatic children (Pope and Dockery 1992. Romieu *et al* 1994 and Neas *et al* 1995). Increased symptoms and bronchodilator usage have also been reported in areas with increased PM_{10} levels (Pope *et al* 1991, Roemer *et al* 1993, Romieu *et al* 1996).

If air pollution in the exposed area was having an effect on the respiratory health of children it seemed the effect was chronic and did not lead to acute exacerbations requiring hospitalisation. There was nevertheless an increase in symptoms and morbidity which led to school absenteeism. It is important not to over-interpret the results of a cross-sectional study, but in 1991 there would appear to have been a child health problem in the exposed area and further studies were required to determine whether airborne pollution was a major contributory factor.

Chapter Five

The significance of cough, wheeze and asthma diagnosis in epidemiological surveys

5.1 Introduction

Many studies have reported the prevalence of asthma and of respiratory symptoms in children (Ninan and Russell 1992, Luyt *et al* 1993, Anderson *et al* 1994). However, it is difficult to compare the results of different prevalence surveys because study populations have different socio-economic profiles, environmental risk factors vary with time and between different areas, and the criteria used to define asthma differ. The pattern of respiratory symptoms can vary depending on the magnitude of specific risk factors in the area surveyed. It is necessary to distinguish which symptoms are associated with which risk factors in order to determine which group(s) of symptoms is/are the best surrogate of asthma and therefore estimate the true prevalence of asthma in groups of children with different respiratory symptom profiles.

This chapter examines questionnaire reported data from the 1991 and 1993 cross-sectional surveys which were performed to assess the possible impact of airborne dust pollution on the respiratory health of primary school children on Merseyside. Children in an area with increased levels of dust pollution had a higher prevalence of excess cough as a solitary symptom compared to children in control areas (Chapter 4/Brabin *et al* 1994). It was not clear whether the increased reporting of excess cough as a solitary symptom represented an increase in asthma or whether it was a non-asthmatic response to increased levels of inhaled dust.

The objectives of this chapter were: (1) To determine the prevalence of cough, wheeze and breathlessness either singly or in combination. (2) To identify whether questionnaire reported excess cough as a solitary symptom has similar risk factors to the questionnaire reported triad of cough, wheeze and breathlessness. (3) To compare the prevalence of diagnosed asthma in children with different symptom profiles.

5.2 Methods

Two cross-sectional surveys of respiratory health in primary school children were performed in 1991 and 1993. The study populations, questionnaire design, data collection procedures and statistical analysis were described in chapter three.

5.3 Results

The proportions of questionnaires returned were similarly high in both surveys, 1872/2035 (92%) in 1991 and 3746/4288 (87%) in 1993. Table 5.1 gives a general description of the study population for each survey. More children were diagnosed asthmatic by a doctor in 1993 but there were no differences in the overall prevalence of symptoms between the surveys.

Table 5.1 General description of children for both surveys

Variable	1991 (n=1872)	1993 (n=3746)
Mean age, yrs (SD)	7.09 (2.0)	7.15 (2.0)
Sex, boy (%)	51.0	50.2
Doctor diagnosed asthma (%)	17.4	22.1***
% living in the area of increased air pollution	25.9	25.0
% with wheezing	20.6	21.3
% with breathlessness	12.8	12.7
% with cough	22.8	23.3

*** $p<0.001$, comparing 1993 with 1991. For other variables there was no significant difference between 1991 and 1993. Wheezing = severe attack of wheezing at any time. Breathlessness = severe attack of breathlessness at any time. Cough = excess cough in the previous 12 months.

The proportion of children with no symptoms (shown in table 5.2 as C-W-B-), with the single symptom of excess cough (EC, shown in table 5.2 as C+W-B-), or with the triad of cough, wheeze and breathlessness (CWB,

shown in table 5.2 as C+W+B+) in combination were also similar in the two surveys.

Table 5.2 Comparison of the prevalence (%) of respiratory symptom profiles in 1991 and 1993

Respiratory symptom profile	1991 (n=1583)*	1993 (n=3083)*
C-W-B-	70.1	69.5
C+W-B-	8.9	9.2
C+W+B+	8.3	7.3
C+W+B-	4.7	4.7
C-W+B-	4.1	5.0
C-W+B+	1.5	1.8
C+W-B+	1.7	1.1
C-W-B+	0.7	1.3

* No. of questionnaires returned with responses for all respiratory variables. C=excess cough in the previous 12 months; B=severe attack of breathlessness at any time; W=severe attack of wheezing at any time. + or - indicates the presence or absence of a symptom. The symptom patterns of cough alone (C+W-B-) and cough, wheeze and breathlessness (C+W+B+) are more common than one would expect if the symptoms were independent of each other. Log linear analysis shows that there is a strong positive association between wheeze and breathlessness (chi^2=443, p<0.001). There is also a positive association between cough and wheeze (chi^2= 197, p<0.001) and between cough and breathlessness (chi^2=104, p<0.001)

Table 5.3 Proportions (%) of different symptom combinations for children with doctor diagnosed asthma

Respiratory symptoms	1991 (n=237)	1993 (n=533)	Significance level (p value)
Cough, wheeze and breathlessness (C+W+B+)	45.6	37.7	0.05
Cough or breathlessness with wheeze (C+B-W+ or C-B+W+)	30.7	32.5	0.71
Cough and/or breathlessness without wheeze (C+B+W- or C+B-W- or C-B+W-)	23.7	29.8	0.09

C=excess cough in the previous 12 months; B=severe attack of breathlessness at any time; W=severe attack of wheezing at any time. + or - indicates the presence or absence of a symptom.

In 1993 children with doctor diagnosed asthma were less likely to have the symptom triad of CWB 37.7% vs 45.6% (p=0.05), and more likely to have been labelled as asthmatic without ever having wheezed 29.8% vs 23.7% (p=0.09) (table 5.3).

UNIVARIATE STRATIFIED ANALYSIS

A comparison of socio-economic and maternal factors in 1991 and 1993 for asymptomatic children and those with EC and CWB is shown in table 5.4. Univariate analysis showed that respiratory symptoms were significantly associated with renting rather than owning a property ($p<0.05$) and with the reported presence of dampness in the home ($p<0.01$), but not with the presence of smokers in the home or with having been breast fed. The symptom triad was significantly associated with having been born prematurely ($p<0.01$).

Table 5.4 Frequency of socio-economic and maternal variables (%) for children with different respiratory symptom profiles

	Respiratory symptom profile		
	Asymptomatic	EC	CWB
1991	n=1109	n=141	n=132
Rented accommodation	41.1	49.3	59.7***
Damp home	12.0	22.5**	31.4***
Smoker(s) in household	58.4	66.4	65.0
Pre-term birth	12.5	13.7	26.0***
Not breast fed	68.2	66.2	67.9
1993	n=2144	n=284	n=224
Rented accommodation	42.9	54.7***	51.6*
Damp home	14.0	27.7***	30.5***
Smoker(s) in household	58.0	60.6	61.2
Mother smoked during pregnancy	36.0	34.3	35.1
Pre-term birth	11.8	11.7	19.4**
Not breast fed	68.1	73.5	65.2

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ - compared with asymptomatic children

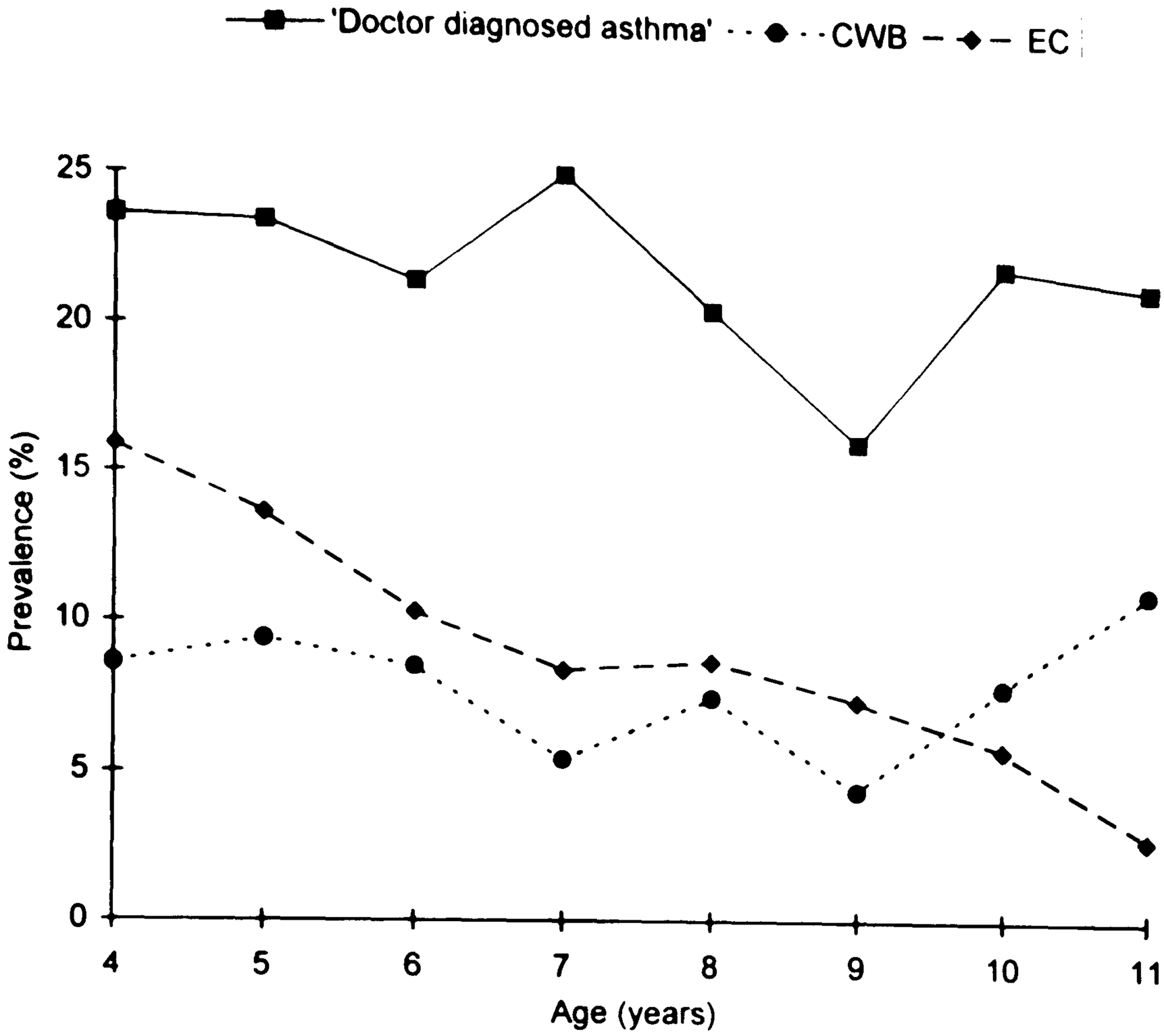


Figure 5.1 Age specific prevalence of 'doctor diagnosed asthma', cough with wheeze and breathlessness (CWB) and excess cough as a solitary symptom (EC).

The age specific prevalence of lifetime diagnosed asthma and CWB did not change. That for EC fell significantly from 14.5% for 4-5 year olds to 5.4% for the 10-11 year olds ($p<0.001$) (figure 5.1).

In both surveys asymptomatic children were less likely to have doctor diagnosed asthma, allergies, medicines prescribed, admissions to hospital for respiratory symptoms, absenteeism from school (for six or more days) due to respiratory symptoms (all $p<0.01$), compared to children with EC or CWB (table 5.5). Children with EC had a lower prevalence of each of these ill-health indicators when compared to children with CWB.

In 1993 the children with EC were more likely to have been diagnosed as asthmatic by a doctor ($p<0.05$), and to report problems with allergies.

Significantly more children with the symptom triad received prescribed medicines in 1993 ($P<0.05$), although 25% were reported to be receiving no medication. In 1991, 2.1% (23/1109) and in 1993, 3.0% (63/2144) of asymptomatic children had a history of doctor diagnosed asthma: None of these children had current symptoms, although 52% in 1991 (12/23) and 38% in 1993 (24/63) had had cough at some time in life which had been diagnosed as asthma. Reported diagnosis of asthma in other asymptomatic children remains unexplained.

Table 5.5 Health parameters (%) in 1991 and 1993 for children with different respiratory symptom profiles

	Respiratory symptom pattern		
	Asymptomatic	EC	CWB
1991	n=1109	n=141	n=132
Doctor diagnosed asthma	2.1	10.0	83.1
Allergies (hayfever, eczema)	8.7	13.3	47.3
Prescribed medicines†	4.4	14.9	61.8
Absent from school due to respiratory symptoms for ≥6 days/yr	0.9	5.7	39.0
Ever admitted to hospital for respiratory symptoms	3.0	25.0	61.0
1993	n=2144	n=284	n=224
Doctor diagnosed asthma	3.0	22.6*	89.9
Allergies (hayfever, eczema)	12.9*	18.8	61.0*
Prescribed medicines	5.2	22.9	75.1*
Absent from school due to respiratory symptoms for ≥6 days/yr	1.5	4.6	36.8
Ever admitted to hospital due to respiratory symptoms	4.1	25.6	61.4

* $p<0.05$ - comparing 1991 with 1993.
† 65% of which are anti-asthmatic medicines.

REGRESSION ANALYSIS

Adjusted odds ratios for risk factors were calculated for respiratory symptom profiles by logistic regression in order to control for multiple confounding factors (table 5.6). Maternal asthma, allergies and other health problems were strongly associated with CWB. Pre-term birth and paternal asthma were associated with cough and wheeze. The risk of cough and wheeze decreased with age (more steeply for cough). Of the other risk factors some were associated with wheeze and some only with cough. Children with environmental risk factors such as going to school in the area of increased dust pollution, dampness in the home and rented accommodation were more likely to have EC as a solitary symptom.

5.4 Discussion

PREVALENCE OF RESPIRATORY SYMPTOM PROFILES

Questionnaires are often used in respiratory health surveys and data collected in this way have been shown to be reproducible (Brunekreef *et al* 1992, Peat *et al* 1992b, Cunningham *et al* 1994). Confidence that the information collected is valid is dependent upon response rates, which in these surveys compared favourably with other reports (Andrae *et al* 1988, Ninan and Russell 1992, Luyt *et al* 1993, Anderson *et al* 1994).

Both surveys were performed in parallel in the same areas and in the same months (October to December), reducing variations due to seasonal influences. The prevalence of wheezing, cough, and breathlessness, is comparable with previous reports (Ninan and Russell 1992, Luyt *et al* 1993). Mitchell *et al* (1989), Schwartz *et al* (1990) and Halfon *et al* (1993) have reported that lower social class is associated with increased morbidity and a higher prevalence of asthma. The lifetime prevalence of doctor diagnosed

Table 5.6 Logistic regression models for cough, wheeze and breathlessness for 1993 data

	Respiratory symptom		
	Cough	Wheeze	Breathlessness
Variable	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Child has allergies	3.29 (2.50-4.33)	4.47 (3.36-5.94)	5.26 (3.79-7.29)
Maternal asthma	1.67 (1.65-2.43)	2.71 (1.87-3.93)	2.87 (1.91-4.33)
Child has other health problems	1.91 (1.44-2.53)	1.82 (1.34-2.46)	1.65 (1.10-2.46)
Age in years	0.83 (0.78-0.88)	0.92 (0.87-0.97)	0.99 (0.93-1.06)
Pre-term birth	1.65 (1.24-2.20)	1.46 (1.08-2.00)	1.38 (0.95-1.99)
Paternal asthma	1.43 (0.96-2.12)	1.71 (1.13-2.58)	1.25 (0.75-2.08)
Sex (girl)	0.83 (0.67-1.03)	0.79 (0.63-1.00)	0.91 (0.69-1.19)
Father works in dusty environment	1.15 (0.90-1.48)	1.64 (1.27-2.12)	1.13 (0.82-1.55)
Unemployed mother	1.31 (1.01-1.68)	1.28 (0.97-1.68)	1.11 (0.80-1.55)
School in area of increased dust pollution	1.46 (1.14-1.87)	1.22 (0.93-1.60)	1.28 (0.93-1.78)
Damp home	1.56 (1.19-2.04)	1.24 (0.92-1.62)	1.25 (0.88-1.78)
Rented accommodation	1.32 (1.08-1.60)	1.08 (0.83-1.39)	0.88 (0.64-1.21)

asthma is higher than reported elsewhere, though this may be confounded in part by the low social class of the three areas in this study.

Hospital admission rates are a marker of asthma severity, and school absenteeism for respiratory symptoms is a useful indicator of respiratory morbidity, (Hill *et al* 1989a, Anderson *et al* 1994). Absences from school (for more than 6 days) due to respiratory symptoms and admissions to hospital due to respiratory symptoms declined slightly between 1991 and 1993.

Excess cough as a solitary symptom is more common in younger children, this may reflect the occurrence of respiratory infections or structural differences in airway size. The age specific prevalence of CWB does not seem to fluctuate which may be due to the persistent nature of the symptom combination.

RISK FACTORS FOR SYMPTOM PROFILES

There are reports of strong associations of childhood respiratory symptoms with passive smoking especially in susceptible children (Charlton 1984, Duff *et al* 1993, Braback *et al* 1995, Stoddard and Miller 1995). The magnitude of the effect may be dependent on the amount of contact between parent and child, or whether the mother smoked during pregnancy (Tager *et al* 1983, Rona and Chinn 1993, Neas *et al* 1994). Disentangling the effects of mothers smoking during pregnancy and post-natal exposure is difficult as a large proportion of women who smoke whilst pregnant continue to smoke five years later (Taylor and Wadsworth 1987, Frischer *et al* 1992). This analysis did not show an effect of passive smoke exposure on the risk of respiratory symptoms in children even after adjustment for confounding factors related to social and home environment risks. Cook *et al* (1993) reported that reductions in lung function were not related to questionnaire data relating to passive smoke exposure. However when they considered an objective measure of passive smoke exposure (levels of salivary cotinine) an inverse relationship

was shown with indices of lung function. This suggests that the absence of an association between passive smoke exposure and respiratory symptoms in children reflects the lack of sensitivity of questions asked in surveys.

Studies have reported that infants who are breast fed have less allergic disease and respiratory symptoms during early childhood and beneficial effects may continue into adolescence (Woodward *et al* 1986, Wright *et al* 1989, Saarinen and Kajosaari 1995). There was no association between having been breast fed and later childhood respiratory symptoms, similar findings have been reported elsewhere (Fergusson *et al* 1983, Horwood *et al* 1985)

Questionnaire reported damp in the home was associated with the occurrence of cough. Other studies have reported dampness and/or mould to be associated with allergic sensitisation, asthma and respiratory symptoms (Brunekreef *et al* 1989, Platts-Mills *et al* 1992, Verhoeff *et al* 1995). Pre-term birth was a significant risk factor for the development of the symptom triad later in childhood, which has been reported by others (Rona *et al* 1993, Ninan *et al* 1995, Elder *et al* 1996).

ASTHMA DIAGNOSIS

The detrimental effects of air pollution on respiratory health in children have been widely reported (Lunn *et al* 1967, Sultz *et al* 1970, Bobak and Leon 1992, Wang *et al* 1992). In a recent review Burr (1995) suggested that in asthmatic children an increase in the severity, but not the prevalence of respiratory symptoms is associated with air pollution. Several studies have reported cough as the main respiratory symptom associated with high levels of particulate air pollution (Sobral 1989, Dockery *et al* 1989, Braun-Fahrlander *et al* 1992, Pope and Dockery 1992). Chapter four showed that EC as a solitary symptom was associated with living in and attending school in an area with increased levels of dust pollution, the analysis in this chapter confirms

that observation. The single symptom of wheeze and the symptom triad of CWB were not significantly associated with the area of increased dust pollution. CWB correlated best with the features of atopy and with pre-term birth. The difference in risk profiles EC and CWB are consistent whether the data are analysed by simple univariate comparisons or multiple logistic regression. This suggests that these epidemiological classifications may represent distinct clinical entities. Thus if a child has CWB then a diagnosis of asthma seems very probable and conversely the single symptom EC could be a non-specific response to adverse environmental conditions and not represent asthma at all. Although such a hypothesis cannot be answered from cross-sectional data alone the proportions of children with different symptom profiles and doctor diagnosed asthma further supports this proposal. Doctor diagnosed asthma was reported in 83% and 90% of children with CWB in 1991 and 1993, versus 10% and 23% of those with EC and hardly at all in asymptomatic children. Treatment prescribing follows a similar pattern. Thus doctors appear to have recognised a similar distinction in clinical practice.

Between 1991 and 1993 there was a significant increase in the prevalence of diagnosed asthma and also in the number of children receiving medication for asthma. Since overall symptom prevalence was unchanged, this suggests a change in medical behaviour. The increase in labelling was most marked in children with EC with more than twice as many being diagnosed as asthmatic, and if allowance is made for the non-asthma medication being unchanged, nearly twice as many received asthma therapy. In 1993, 1 out of 8 children that doctors had diagnosed as asthmatic had been diagnosed on the basis of the single symptom of cough. Whether these children really have asthma warranting treatment or whether doctors have become more aware of, and more aggressive towards, cough as a marker of asthma remains unknown. Possibly doctors use cough together with auscultation of the chest to reach a diagnosis.

If the index of asthma in this survey had been `doctor diagnosed asthma' an increase in asthma in real terms of 4.7% over 2 years (17.4%-22.1%) would be reported, which since overall symptom prevalence was unchanged, would have been misleading.

In conclusion, it is proposed that the symptom triad of cough, wheeze and breathlessness occurring in a child may be a better marker of true asthma in epidemiological surveys than either relying on single symptoms or upon doctor diagnostic patterns. Since asthma prevalence is so dependent on the definition used, further studies are needed to either confirm this hypothesis or produce a better version that can be adopted as a standard.

Chapter Six

Temporal changes

6.1 Introduction and objectives

Detailed reviews of the literature suggest that the prevalence of childhood asthma in industrialised countries is rising (Anderson 1993). This conclusion has been drawn from the results of cross sectional surveys performed 10 to 20 years apart using the same methodologies (Burr *et al* 1989a, Ninan and Russell 1992).

In the Bootle Dock area it was expected that there would be a reduction in levels airborne dust pollution between 1991 and 1993 as a consequence of environmental protection measures and relocation of steam coal stockpiles a further 200 metres away from residential areas. In 1991, excess cough as a solitary symptom (EC) and the symptom triad of cough with wheeze and breathlessness (CWB) were shown to have a higher prevalence in the dock area, exposed to dust pollution compared to areas with lower urban levels of dust pollution (Brabin *et al* 1994/Chapter four). Milligan *et al* (unpublished findings) have shown a linear and spatial relationship between the prevalence of EC mapped by each child's residential postcode and proximity to the dock area.

The objective of this chapter was to describe short-term changes between 1991 and 1993 in 'doctor diagnosed asthma', respiratory symptoms, socio-demographic factors and air quality for children living in the area exposed to airborne dust pollution and the two control areas. A longitudinal cohort was identified of children surveyed in 1991 who attended the same school in 1993.

The specific objectives were to determine: (1) Cross-sectional differences in socio-demographic, respiratory and pollution indicators between the two surveys. (2) Incidence and recovery rates for specific respiratory symptoms.

6.2 Methods

STUDY GROUPS

In 1991 and 1993 questionnaires were sent to the parents/guardians of 2035 and 3026 children in the cross-sectional surveys. In 1993 a cohort of 1202 children who had been studied in 1991 were re-surveyed.

Dust pollution levels were measured as outlined in chapter three by the Public Protection Department.

EpiInfo was used for univariate comparison of cross-sectional data, and the Statistical Package for Social Sciences (SPSS) was used to apply the McNemar test for longitudinal data.

6.3 Results

There was no difference in questionnaire response rates between the surveys, 92% (1872/2035) in 1991 and 88% (2652/3026) in 1993 for the cross-sectional surveys and 91% (1093/1202) for the longitudinal cohort.

6.3.1 Cross-sectional analysis

SOCIO-DEMOGRAPHIC FACTORS

Between survey changes in socio-demographic factors are shown in table 6.1. Levels of parental employment fell significantly in both control and exposed areas. The proportion of families living in rented accommodation and damp homes increased significantly in control areas. There were no significant changes between 1991 and 1993 in parental smoking, pet ownership, premature birth or breastfeeding in either control or exposed areas, although reported smoking prevalence In 1993 in the exposed area was significantly higher than in the control areas.

RESPIRATORY INDICATORS, SYMPTOM PROFILES AND SEVERITY

Cross-sectional prevalence for respiratory indicators are shown in table 6.2. There were significant differences between surveys in the prevalence of doctor diagnosed asthma, prescribed asthma treatment, maternal asthma, absences from school for six days or more in the previous 12 months due to respiratory symptoms and hospital admissions due to respiratory symptoms in the control areas. More parents reported that their child's asthma was well controlled in 1993 compared to 1991 this difference reached statistical significance in the exposed area. The proportion of children with allergies increased in both control and exposed areas. There were no between survey changes in the prevalence of bronchitis (12.0% and 12.8%), croup (14.0% and 13.4%), paternal asthma (7.1% and 7.8%) and other health problems (24.2% and 24.8%) in control and exposed areas respectively.

In the control areas there were between survey increases in the 12 month period prevalence of wheeze ($p=0.06$), breathlessness ($p<0.05$) and cough ($p<0.01$). The proportion of children who experienced 12 or more attacks of wheeze in the previous 12 months increased ($p<0.01$), as did the prevalence of those who had attacks of cough lasting for more than one hour ($p<0.001$). There were no temporal changes in the severity of symptoms in the exposed area. The proportion of children with recent (previous 12 months) wheeze, cough, attacks of breathlessness more than 12 times per year and prolonged attacks of cough remained higher in exposed areas compared to controls (all $p<0.01$).

The two commonest respiratory symptom patterns were excess cough as a solitary symptom (EC, shown in table 6.3 as C+W-B-) and the symptom triad of cough, wheeze and breathlessness (CWB shown in table 6.3 as C+W+B+). The prevalence of EC was higher and of asymptomatic (C-W-B-)

Table 6.1 Socio-demographic factors (%) in control and exposed areas in 1991 and 1993 (cross-sectional analysis)

Variable	Control areas			Exposed area		
	1991 (n=1348)	1993 (n=1936)	p value	1991 (n=474)	1993 (n=668)	p value
Smokers in household***	59.5	57.8	NS	70.6	68.0	NS
Mother smoked during pregnancy†***	--	34.8	--	--	44.3	--
Father smoked during pregnancy†***	--	48.5	--	--	57.6	--
Pet ownership	56.8	55.7	NS	54.4	55.9	NS
Employed father***	71.0	64.6	<0.001	59.5	52.2	<0.05
Employed mother***	44.6	39.4	<0.01	27.4	27.3	NS
Households without paid income***	25.2	26.8	NS	30.8	37.0	<0.05
Rented accommodation***	39.5	43.9	<0.05	64.5	63.1	NS
Damp home	13.7	17.9	<0.01	21.4	21.3	NS
Sex, boy	50.0	48.4	NS	53.7	56.0	NS
Age, years (SD)	7.6 (2.0)	7.2 (2.1)	NS	7.7 (2.0)	7.2 (2.0)	NS
Birthweight, kg (SD)	3.3 (0.58)	3.4 (0.57)	NS	3.3 (0.60)	3.3 (0.59)	NS
Premature birth	14.3	13.2	NS	15.2	13.5	NS
Breastfed***	35.4	32.9	NS	25.3	22.1	NS

*** $p<0.001$ for exposed *vs* control areas in 1993. † Data available for 1993 only.

Table 6.2 Prevalence (%) of respiratory indicators in control and exposed areas in 1991 and 1993 (cross-sectional analysis)

Variable	Control areas			Exposed area		
	1991 (n=1348)	1993 (n=1936)	p value	1991 (n=474)	1993 (n=668)	p value
Doctor diagnosed asthma	16.2	22.0	<0.001	21.1	21.8	NS
Wheeze in previous 12 months	12.7	15.6	NS	20.3	18.4	NS
Breathlessness in previous 12 months	8.0	10.1	<0.05	16.0	12.4	NS
Cough in previous 12 months **	18.8	22.5	<0.01	34.4	32.5	NS
Attack of wheeze >12 times in past 12 months	3.1	4.9	<0.01	5.9	6.3	NS
Attacks of breathlessness >12 times in past 12 months **	3.0	3.5	NS	5.9	5.8	NS
Attacks of cough lasting for >1hour **	6.4	10.3	<0.001	13.9	14.1	NS
Prescribed asthma treatment	7.4	11.1	<0.001	11.4	11.9	NS
Well controlled asthma	84.9	89.7	NS	72.1	83.9	<0.05
Allergies	14.7	22.6	<0.001	13.6	20.5	<0.01
Maternal asthma	6.8	9.8	<0.01	7.5	8.6	NS
Absence from school for ≥6 days due to respiratory symptoms in past 12 months	11.6	14.9	<0.05	21.2	20.1	NS
Hospital admission in past 12 months due to respiratory symptoms	4.9	7.0	<0.05	5.8	5.3	NS

** p <0.01 exposed vs control area for 1993.

Table 6.3 Prevalence (%) of respiratory symptom patterns in control and exposed areas in 1991 and 1993

Symptom pattern	Controls			Exposed		
	1991 (n=1182)	1993 (n=1639)	p value	1991 (n=400)	1993 (n=538)	p value
C+W-B- ***	7.0	8.8	NS	14.5	15.1	NS
C+W+B+	6.6	7.5	NS	13.5	9.1	<0.05
C+W+B-	4.7	4.5	NS	4.5	5.4	NS
C-W+B-	4.2	5.6	NS	3.8	3.5	NS
C+W-B+	1.2	0.9	NS	3.3	0.9	NS
C-W-B+	0.6	1.5	NS	0.7	0.7	NS
C-W+B+	1.4	1.9	NS	1.8	2.0	NS
C-W-B- **	74.2	69.4	<0.01	57.8	63.2	NS

*** P<0.001 ** p<0.01 exposed vs control areas for 1993.
C=excess cough in the previous 12 months, W=wheezing at any time, B=breathlessness at any time. + or - denotes the presence or absence of a symptom.

children lower in the dust exposed area compared to control areas. Between surveys there was a significant fall in the prevalence of CWB 13.5% vs 9.1%, p<0.01) in the exposed area and in the proportion of asymptomatic children (74.2% vs 69.4, p<0.01) in control areas.

DUST POLLUTION

In 1991 the dust deposition rate in the exposed area was more than six times that in the control areas. Between surveys there was a 26.4% reduction in dust levels in the exposed area (table 6.4).

Table 6.4 Dust deposition rates for control and exposed areas in 1991 and 1993

	Controls		Exposed	
	1991	1993	1991	1993
Dust deposition rates ($mg/m^2/day$)	22.9	26.4	146.1	107.5

6.3.2 Longitudinal cohort

In 1991 and 1993 the mean ages of the longitudinal cohort were 6.72 years (SD 1.44) and 8.78 years (SD 1.45) respectively. Results of the McNemar test comparing socio-economic and respiratory indicators for the longitudinal cohort are shown in table 6.5. There were significant increases in paternal unemployment, allergies (including hayfever and eczema), maternal asthma and lifetime diagnosis of asthma. There were significant reductions in parental smoking and excess cough (either on its own or in combination with other symptoms). There were no differences in the proportion of girls (49.9%), mean birthweight (3.32 Kg, SD 0.58), premature birth (13.6%), breastfeeding (35.6%), paternal asthma (6.9%), other health problems (22.8%), wheezing (20.4%), breathlessness (11.6%), school absence for six days or more due to

respiratory symptoms (15.0 %), dampness in the home (14.3%) and rented accommodation (40.0%).

Table 6.5 Prevalence (%) of socio-economic and respiratory indicators in 1991 and 1993 for the longitudinal cohort

Variable	1991	1993	p value *
Unemployed father	27.3	32.3	<0.001
Smokers in household	59.8	55.9	<0.001
Allergies	18.1	22.8	<0.001
Ever diagnosed asthma	16.7	21.9	<0.001
Excess cough	28.0	25.2	<0.05
Maternal asthma	5.9	8.6	<0.001

* McNemar test

NATURAL HISTORY OF SYMPTOMS (INCIDENCE AND RECOVERY RATES)

The incidence rate was 0.5% per year for CWB, and 2.3% per year for EC. Over two years 52.1% of children with EC and 3.4% of children with CWB recovered. 12.3% of children with EC and 41.4% of those with CWB did not recover. The remaining children had other symptom combinations (table 6.6).

Table 6.6 Incidence and recovery rates, %/2 years (number)

	1993 symptom profile			
	Asymptomatic	EC	CWB	Other symptoms
1991 symptom profile				
Asymptomatic (n=597)	86.8 (518)	4.5 (27)	1.0 (6)	7.7 (46)
EC (n=73)	52.1 (38)	12.3 (9)	2.7 (2)	32.8 (24)
CWB (n=58)	3.4 (2)	3.4 (2)	41.4 (24)	51.7 (30)

6.4 Discussion

Other studies which have described temporal changes in asthma prevalence have been performed 10 to 20 years apart (Burr *et al* 1989a,

Ninan and Russell 1992). This analysis examines short-term changes (over two years) in the respiratory health of primary school children. It is comparable to studies by Hill *et al* (1989b) and Brooke *et al* (1995) who performed cross sectional surveys in children three years apart. The present surveys were performed at the same time of year (October to December), to avoid seasonal variations. The questionnaire used had previously been shown to be reproducible (Clifford *et al* 1989) and response rates in both surveys were good and are comparable to other studies (Hill *et al* 1989a, Ninan and Russell 1992, Luyt *et al* 1993 and 1994, Austin *et al* 1994, Omran and Russell 1996).

SOCIO-DEMOGRAPHIC CHANGES

Changes in factors associated with social deprivation such as parental unemployment, rented housing and damp homes indicated that children from families in the 1993 study were worse off compared to those in 1991. Such changes in socio-economic factors may be explained by the transient nature of this largely inner city population. This data shows that the exposed dock area was more socially deprived, with higher proportions of parents smoking (including during pregnancy), unemployment and rented accommodation than in control areas. Socio-economic and respiratory changes in the longitudinal cohort were similar those observed in the cross-sectional study.

RESPIRATORY INDICATORS

In control areas there were significant differences between surveys in the prevalence of labelled asthma and prescribed asthma treatment. There were also increases in indicators of morbidity such as school absenteeism and hospital admissions for respiratory symptoms. Strachan *et al* (1994) reported that increased respiratory morbidity was associated with poorer families, although there was no difference in diagnosis rates and prescribed

treatment between social classes. In the exposed area a higher proportion of parents perceived their child's asthma to be well controlled in 1993 compared to 1991. The proportion of children with school absences due to respiratory symptoms remained high and greater in the exposed area compared to the control areas.

DIAGNOSED ASTHMA

The increase in the prevalence of 'doctor diagnosed asthma' in the control areas over the two year period may be due to a greater awareness of general practitioners with an increased probability of asthma diagnosis. Before such awareness under-diagnosis of asthma was common (Speight *et al* 1983) and the use of 'doctor diagnosed asthma' in prevalence surveys lead to an underestimation, compared to the prevalence of current wheeze as a marker of asthma. Responses to questionnaires about 'doctor diagnosed asthma' may be influenced by parental recall, diagnostic labelling by the medical practitioner, parental acceptance of the label and access to health care facilities (Peat *et al* 1992b). In addition to questionnaire data objective measures of respiratory function are important when attempting to determine the true prevalence of asthma, although such measures also have their own inaccuracies and reproducibility problems.

SYMPTOM SEVERITY

Hill and colleagues (1989b) suggested that the increased use of asthma as a diagnostic label is unlikely to be due to an increase in the severity of symptoms as the distribution of frequency of attacks did not alter over the three year period of their study. Anderson *et al* (1994) observed an increase in the period prevalence of wheeze and a reduction in severity over a 13 year period which they proposed may be due to improved treatment. In

contrast, a study of Aberdeen schoolchildren showed an increase in the frequency of attacks of wheeze and breathlessness over a five year period (Omran and Russell 1996). There was an increase in the period prevalence of cough and breathlessness, frequency of attacks of wheeze and intensity of cough attacks in the control areas which indicated an increase in symptom severity. The 12 month period prevalence of wheeze in the present study was comparable to reports in other UK studies, (Hill *et al* 1989b, Strachan *et al* 1994, Powell and Primhak 1996a).

There were substantial reductions in the levels of atmospheric dust pollution in the exposed area. If respiratory symptoms were exacerbated by air pollution and air quality improved between 1991 and 1993 a reduction in symptom severity would be expected. In the dust exposed area there was a reduction in the prevalence of CWB, but not of EC which has been shown to be associated with dust exposure (Kelly *et al* 1996/Chapter five). There was no reduction in symptom severity in the exposed area. Although a reduction in dust levels occurred between surveys in the exposed area, dust pollution levels remained high and were higher compared to the control areas. This suggests that if symptom prevalence and severity are linked to dust pollution then further improvements in air quality are needed in the exposed area.

INCIDENCE AND RECOVERY RATES

There have been several community based surveys in children which suggest that asthma improves over time, although Kelly *et al* (1987) indicated that symptoms may return in adult life. Nakadate and Kagawa (1992) reported that peripheral pulmonary function in children with a history of asthma, even if they had been in remission for several years, was reduced compared to control children. In a community study of pre-school children, Brooke *et al* (1995) reported that 7.2% of those with cough (without wheeze) went on to

develop wheeze three years later. The present results showed that over one quarter of children with EC developed other symptoms within two years. Powell and Primhak (1996a) reported that children with wheeze were more likely to retain their symptoms than those with cough. In this analysis it was observed that the symptom triad was persistent, with a low recovery rate, whilst EC was transitory with half of the children recovering within two years.

In recent years other studies have reported increases in persistent wheeze (Anderson *et al* 1994, Rona *et al* 1995) and it is possible that a reduction in the recovery rates from asthma or wheezing illness, rather than a rising incidence, may be responsible for the rising prevalence of asthma. In order to examine this hypothesis, further studies are required to examine sequential incidence and recovery rates in relation to changing patterns of air pollution.

Chapter Seven

Maternal asthma, pre-term birth and the risk of respiratory morbidity in childhood

7.1 Introduction and objective

In a study of children born in a one week in 1970, wheezing at age five was reported to be more common in children who were born prematurely or who were of low birthweight (Golding and Butler 1986). There are a number of possible explanations for this: small, premature infants are more prone to respiratory illnesses in early life which can result in airflow obstruction and impaired lung function (Shaheen and Barker 1994). There is an effect of maternal smoking on pre-term delivery, low birthweight and infant lung function (Marsh *et al* 1994). Children of asthmatic mothers are at increased risk of atopic disease and bronchial hyperreactivity (Bertrand *et al* 1985, Cookson *et al* 1992), and it has been suggested that maternal asthma may predispose to premature labour (Bertrand *et al* 1985, Doucette and Bracken 1993, Patlow *et al* 1992). Hyperactivity of uterine smooth muscle could occur in women with bronchial hyper-responsiveness and β-agonists might be beneficial in prolonging gestation (Schatz *et al* 1990). There is some evidence that asthmatic mothers not requiring inhaled β-agonist bronchodilators during pregnancy have a higher incidence of low birthweight babies (Lao and Huangshung 1990).

None of these studies report on respiratory outcome in children for whom both perinatal outcome, parental history of asthma and smoking during pregnancy are known.

In addition to data on respiratory factors and environmental exposures data was also collected on perinatal outcome (shown as prematurity and birthweight) as well as current respiratory symptoms at 5-11 years of age. The objective of the analysis in this chapter was to determine the impact of maternal asthma on prematurity and birthweight and the effect of all of these factors on the subsequent development of respiratory symptoms in these children.

7.2 Methods

The methods used for data collection were fully described in Chapter three. In addition to data on respiratory symptoms and socio-economic factors we asked about birth factors. Prematurity was determined with the question "Was your baby born prematurely?", birthweight was also requested. In this analysis asthma was identified as reporting of 'doctor diagnosed asthma', or by that of the symptom triad of cough with wheeze and breathlessness (CWB) which we have previously proposed as a surrogate for childhood asthma (Chapter 5/Kelly *et al* 1996).

BIRTHWEIGHT AND GESTATIONAL AGE CATEGORIES

Children were defined as low birthweight if <2.5 Kg at delivery and pre-term according to the parental response to the prematurity question. Small for gestational age (SGA) infants were those reported as full-term babies but <2.5 Kg birthweight.

STRATIFIED ANALYSIS

Contingency tables were analysed using hierarchical log linear modelling. Odds ratios calculated for the main effects of interest were adjusted for confounders using logistic regression. Potential confounders were of three main types: socio-economic, environmental and factors related to predisposition. The Statistical Package for Social Sciences (SPSS) was used for data analysis.

7.3 Results

In 1991 a total of 1872 questionnaires were returned out of 2035 sent to parents (92%). In the second survey in 1993 a total of 3746 out of 4288 sent to parents were returned (87%). A cohort of 1093 children were surveyed on both occasions. Of the 1991 respondents 97.1% answered the question on

pre-term delivery and 95.9% provided their child's birthweight. In 1993 the figures were 97.4% and 96.8% respectively. Response rates for the main respiratory variables in 1991 were 89.5% (doctor-diagnosed asthma), 85.8% (wheezing), 86.6% (breathlessness) and 90.1% (cough). Very similar response rates were observed for the 1993 survey. For parents who completed the questionnaire in both surveys the agreement between answers on prematurity and birthweight were 97% and 78% respectively. The mean difference in birthweights that did not match was small (168g). The agreement for respiratory factors were doctor-diagnosed asthma (93.1%), wheezing (69.9%), breathlessness (62.1%), maternal asthma (89.7%) and paternal asthma (77.8%).

MATERNAL ASTHMA AND PRE-TERM BIRTH

In both surveys there was a significant increase in reported pre-term delivery associated with maternal but not paternal asthma (table 7.I). The prevalence of pre-term delivery among the 2652 children surveyed in 1993 but not in 1991 was 17.1% for asthmatic and 13.0% for non-asthmatic mothers.

Children in the 1993 survey were separated into four birth categories determined by birthweight, <2.5kg or ≥2.5kg and pre-term or full-term. Significantly more pre-term babies were born to asthmatic mothers (table 7.2), but amongst these pre-term babies asthma does not significantly increase the risk of low birthweight (<2.5kg). The mean birthweight of pre-term babies over 2.5 Kg was 2.62 (0.64, SD) which corresponds to a 50th percentile at 34.5 weeks gestation on the standard growth charts (Tanner and Thomson 1970). There was no difference in the prevalence of growth retarded babies (full-term gestation and <2.5kg) in relation to parental asthmatic status. The mean birthweights for growth retarded full-term (SGA) and normal full-term infants were 2.25 Kg (0.19, SD) and 3.47 Kg (0.46, SD) respectively.

Table 7.1 The prevalence of pre-term delivery in 1991 and 1993 in relation to parental asthma

Survey group and year	Prevalence of pre-term delivery %	
	Parent asthmatic	Parent non-asthmatic
1991		
Mother	23.7 (28/118)	14.0 (220/1574)
Father	16.7 (17/102)	14.1 (220/1559)
1993		
Mother	19.1 (61/319)	13.0 (410/3158)
Father	14.7 (34/232)	13.2 (405/3066)

Parenthesis: numbers surveyed

The mean birthweights of children whose mothers smoked during pregnancy was significantly less compared to those whose mothers did not smoke during pregnancy (3.196 kg vs 3.408 kg, $p<0.001$). Maternal asthma and smoking during pregnancy each increased the risk of pre-term delivery.

Table 7.3 shows the unadjusted odds ratios for the various categories of mothers. Asthmatic mothers who smoked were at the highest risk of delivering pre-term and non-asthmatic non-smoking mothers were at the lowest risk.

Table 7.3 Odds ratio for pre-term delivery among mothers in relation to asthmatic status and cigarette smoke exposure during pregnancy

Maternal asthmatic and pregnancy smoking status	Prevalence (%) of pre-term delivery	Unadjusted Odds Ratio (95% C.I.)
Asthmatic and smoker	19.8	1.91 (1.18-3.06)
Asthmatic and non-smoker	17.5	1.63 (1.07-2.49)
Non-asthmatic and a smoker	15.3	1.39 (1.11-1.73)
Non-asthmatic and non-smoker	11.5	-

* Compared to non-asthmatic, non-smoking mothers

Table 7.2 Prevalence of pre-term, growth retarded and full-term deliveries in relation to parental asthmatic status (1993 survey)

	Asthmatic Parent					*Non-Asthmatic Parent*			
Parent	*Full-term*		*Pre-term*			*Full-term*		*Pre-term*	
	<2.5kg˙	*≥2.5kg*˙˙	*<2.5kg*	*≥2.5kg*		*<2.5kg*˙	*≥2.5kg*˙˙	*<2.5kg*	*≥2.5kg*
Mother	3	253	24	37		58	2657	162	243
[n=317]	(0.9)	(79.8)	(7.6)	(11.7)	[n=3120]	(1.9)	(85.1)	(5.3)	(7.8)
Father	2	193	13	21		54	2573	155	247
[n=229]	(0.9)	(84.3)	(5.7)	(9.2)	[n=3030]	(1.8)	(84.9)	(5.1)	(8.2)

Numbers in parenthesis are percentages

˙ Small for gestational age (full term and <2.5kg birthweight)

˙˙ Appropriate for gestational age (full term and ≥2.5kg birthweight)

Associations among pre-term delivery, low birthweight (<2.5kg), paternal and maternal asthma were assessed by log-linear analysis of the 4-way table. The best fitting hierarchical model showed 2 significant associations: pre-term birth and low birthweight ($p<0.001$); maternal asthma and pre-term birth ($p=0.021$).

Logistic regression was used to calculate adjusted odds ratios for the effects of smoking and asthma. This was done separately for the 1991 and 1993 surveys (table 7.4). In both 1991 and 1993 maternal asthma was the predominant risk factor for pre-term delivery. Any smokers in the

Table 7.4 Adjusted odds ratio for pre-term delivery from multiple logistic regression

Variable	*Odds Ratio*	*95% Confidence Interval*
1991 Survey (n=1715)		
Maternal asthma	1.89	1.21-2.96
Any smokers in household	1.64	1.22-2.19
1993 Survey (n=3403)		
Maternal asthma	1.49	1.10-2.02
Mother smoked during pregnancy	1.35	1.10-1.65

household was the only other significant risk factor identified for the 1991 model. The 1993 survey showed that it was maternal smoking during pregnancy, rather than passive smoke from fathers or others in the household, which was directly associated with increased risk of pre-term delivery. There was no statistical interaction between maternal asthma and smoking, indicating they have separate effects. Other health problems, allergies and paternal unemployment though significant when considered in isolation did not have odds ratios significantly different from unity after adjustment for known confounders. Information on maternal parity and age was not available on the questionnaire and could not be added to the model. Maternal smoking during pregnancy was associated with an increased risk of delivering a baby that was small for gestational age, although not significantly (odds ratio 1.63, 95% CI, 0.97-2.73).

PARENTAL ASTHMA, BIRTHWEIGHT, PREMATURITY AND LATER CHILDHOOD RESPIRATORY MORBIDITY

Table 7.5 shows the prevalence of labelled asthma and CWB by parental asthma status and whether or not a child was born pre-term. Adjusted odds ratios were estimated using logistic regression analysis and showed an effect of maternal asthma (OR, 95% CI; 3.13, 2.36-4.16); paternal asthma (2.23, 1.62-3.05) and pre-term birth (1.40, 1.10-1.79), on increasing the risk of the child having diagnosed asthma. Using the CWB asthma surrogate, the analysis showed a similar pattern; maternal asthma (OR, 95% CI; 3.30, 2.17-5.03), paternal asthma (1.94, 1.16-3.25) and pre-term birth (1.89, 1.29-2.76). A number of environmental, socio-economic and predisposing factors contribute to the risk of respiratory morbidity in children.

Table 7.5 Prevalence (%) of respiratory morbidity in children in relation to prematurity by parental asthmatic status, 1993 survey

Parental asthmatic status and childhood respiratory outcome	Birth category: Full-term	Birth category: Pre-term
Asthmatic mother		
Doctor diagnosed asthma	41.4 (106/256)	45.8 (27/59)
Cough, wheeze and breathlessness	17.8 (35/197)	16.3 (7/43)
Asymptomatic	49.2 (97/197)	53.5 (23/43)
Non-asthmatic mother		
Doctor diagnosed asthma	19.0 (513/2694)	26.7 (102/382)
Cough, wheeze and breathlessness	5.6 (129/2299)	10.5 (35/334)
Asymptomatic	72.6 (1668/2299)	63.2 (211/334)
Asthmatic father		
Doctor diagnosed asthma	36.1 (70/194)	55.8 (19/34)
Cough, wheeze and breathlessness	13.3 (21/158)	25.0 (6/24)
Asymptomatic	52.5 (83/158)	37.5 (9/24)
Non-asthmatic father		
Doctor diagnosed asthma	19.6 (512/2607)	24.9 (99/397)
Cough, wheeze and breathlessness	5.9 (130/2209)	10.3 (34/331)
Asymptomatic	72.3 (1548/2209)	66.2 (219/331)

Parenthesis: number
Cough = excess cough in previous 12 months.
Wheeze = attack of wheeze at any time.
Breathless = attack of breathlessness at any time.

These include other allergies and health problems, young age, sex (boy), parental unemployment, household dampness, rented accommodation, and geographical area. Adjusting for each of these variables the odds ratio for lifetime asthma diagnosis in pre-term babies was 1.41 (1.06-1.87), and for developing CWB 1.82 (1.15-2.88). Smoking during pregnancy or passive smoking was not associated with any of the respiratory outcome variables in univariate tests in the 1993 data. It is therefore not an important confounder for the relationship between pre-term birth and later respiratory symptoms.

Table 7.6 shows that infants in our survey born small for gestational age to either asthmatic or non-asthmatic parents are at reduced risk of developing asthmatic respiratory symptoms compared to normal birthweight full-term babies. This difference does not reach statistical significance; the odds ratio for having diagnosed asthma was 0.63 (95% CI, 0.28-1.41), and for developing CWB 0.37 (0.05-2.73). These findings are of interest as the reduction in risk is cons nt in the different groups and contrasts with the results for pre-term infants.

7.4 Discussion

QUESTIONNAIRE

Studies which rely on self administered questionnaires are limited by the reliability and validity of the instruments used. Brunekreef *et al* (1992) and Peat *et al* (1992b) reported that questions about doctor diagnosed asthma, wheeze and breathlessness had good reproducibility. In contrast, Anderson *et al* (1992) in a report on the National Child Development Study found that lifelong reports of asthma and reports over the previous year did not show good agreement. The validity of the survey is dependent on the response rate and the high 92% and 87% compliance figures compare favourably with other

Table 7.6 Prevalence (%) of respiratory morbidity in children in relation to foetal growth retardation by parental asthmatic status, 1993 survey

Parental asthmatic status and childhood respiratory outcome	Birth category	
	Full-term (≥2.5kg)	Full-term (<2.5kg)*
Asthmatic mother		
Doctor diagnosed asthma	41.9 (103/253)	0.0 (0/3)
Cough, wheeze and breathlessness	17.9 (35/196)	0.0 (0/1)
Asymptomatic	49.4 (97/196)	0.0 (0/1)
Non-asthmatic mother		
Doctor diagnosed asthma	19.2 (506/2636)	13.8 (8/58)
Cough, wheeze and breathlessness	5.7 (128/2251)	2.1 (1/48)
Asymptomatic	72.5 (1633/2251)	72.9 (35/48)
Asthmatic father		
Doctor diagnosed asthma	36.5 (70/192)	0.0 (0/2)
Cough, wheeze and breathlessness	13.4 (21/157)	0.0 (0/1)
Asymptomatic	52.2 (82/157)	100.0 (1/1)
Non-asthmatic father		
Doctor diagnosed asthma	19.8 (505/2553)	13.0 (7/54)
Cough, wheeze and breathlessness	6.0 (129/2164)	2.2 (1/45)
Asymptomatic	72.4 (1566/2164)	71.1 (32/45)

* Small for gestational age
Parenthesis: number
Cough = excess cough in previous 12 months.
Wheeze = attack of wheeze at any time.
Breathless = attack of breathlessness at any time.

surveys (Clifford *et al* 1989, Ninan and Russell 1992, Luyt *et al* 1993) and reduces the effects of bias. Over 95% of the respondents answered the key questions relating to pre-term delivery and birthweight. For all the main respiratory symptom variables response rates were over 85%. The measure of agreement for important measures in those who completed both surveys was generally good, although it was only 62.1% for breathlessness. Ascertainment of prematurity by the question 'Was your baby born prematurely?' is dependent on the mother's knowledge and understanding of gestational age at delivery, which may have been explained in a number of ways by the attending doctor, midwife or nurse. The validity of the answers is

supported by the observation that the mean birthweight of babies greater than 2.5 kg and reported as pre-term by the mother was 2.62 Kg. This corresponds to the 50th percentile at 34.5 weeks gestation on the standard growth charts (Tanner and Thomson 1970). Only 4 pre-term infants were above the 97th centile for birthweight at 37 weeks gestation. This distribution of birthweights for the pre-term group is comparable to reference percentiles for premature babies and supports the validity of parental recognition of pre-term delivery. Further to this Seidman *et al* (1987) reported that 75% of mothers recalled birthweight within 100g and gestational age within one week compared to hospital records. Another study reported that ten years after delivery 90% of mothers placed their child into the correct birthwieght category (Tilley *et al* 1985). The prevalence of reported pre-term delivery was 14% in the 1991 survey and 13% in the 1993 survey. Both these figures are appreciably higher than previous surveys using prospective data. A stronger case for the causality of the associations would be demonstrated if the validity of the pre-term delivery data was confirmed against original birth registers.

MATERNAL ASTHMA, SMOKING AND PRE-TERM DELIVERY

Biological and obstetric factors can play an important role in determining gestational duration. In a meta-analysis Kramer (1987) identified 43 factors associated with low birth weight or pre-term birth, maternal asthma was not listed as a significant risk factor. This analysis indicates a significant association between maternal asthma and pre-term birth but amongst pre-term births, asthma does not increase the risk of low birthweight. This suggests that the effect of maternal asthma is primarily to shorten gestation to 34-37 weeks rather than leading to very pre-term delivery. The regression analysis which controlled for socio-economic factors identified maternal asthma in both the 1991 and 1993 surveys as a risk factor for pre-term delivery.

Hypotheses to explain the association of maternal asthma and pre-term delivery remain to be elucidated. An attractive theory is that of uterine smooth muscle hyper-reactivity in women with bronchial hyper-responsiveness (Bertrand *et al* 1985). The effect of β-agonists in inhibiting labour supports this hypothesis, and asthmatic patients not using β-agonist bronchodilators during pregnancy have been reported as having a higher incidence of low birthweight babies (Lao and Huangshung 1990). Observations by Doucette and Bracken (1993) and Kramer *et al* (1995) that women with a history of asthma are at higher risk of pre-term delivery further support the bronchial-uterine smooth muscle labilty hypothesis. Conversely, Schatz *et al* (1995) did not show an association between maternal asthma and pre-term delivery, although the women in their study had well controlled asthma. The data cannot address issues such as whether it is asthma severity, or its treatment or control that are important.

The 1991 survey showed smokers in the household as a significant factor increasing risk of pre-term delivery. The greater detail on parental smoking collected in 1993 showed that maternal smoking during pregnancy was the important risk factor and not the passive effects of others smoking. The effects of maternal asthma and maternal smoking appear to have independent and separate effects on increasing the incidence of prematurity. There is a large amount of literature on maternal smoking as an adverse factor on intrauterine growth and gestational duration. The data shows that children born to mothers who smoked during pregnancy had mean birthweights 212g less than those whose mothers did not smoke. This reduction in birthweight is of a similar order of magnitude as reported elsewhere (Brooke *et al* 1989, Conter *et al* 1996). Fox *et al* (1994) reported that the decrement in mean birthweight associated with smoking during pregnancy increased with maternal age. In mothers of 40 or more they showed a difference of 376g compared to reduction of 117g in younger

mothers of 17 years of age. Studies on the effects of passive smoking on birth weight and gestational age are less consistent. Ahlberg and Bodin (1991) reported a weak association between environmental tobacco smoke (ETS) exposure in the workplace and increased risk of pre-term birth but no effect on birthweight. Fortier *et al* (1994) and Zhang *et al* (1996) reported that passive smoking was associated with a reduction in birthweight, the size of the effect being two to ten times smaller than that of active smoking. In contrast, Ogawa *et al* (1991) found no association between ETS exposure and reduced birthweight.

Maternal smoking exerts its effects on foetal growth retardation by leading to intrauterine hypoxia. Such mechanisms involve the formation of carboxyhaemoglobin which reduces the oxygen carrying capacity of the blood, catecholamine release which leads to uterine vasoconstriction and disruption of placental ultrastructure (Quigley *et al* 1979, Abel 1980, Asmussen 1980).

Maternal smoking was not associated with an increased risk of delivering a small for dates baby although the confidence interval for the odds ratio was close to significance (0.97-2.73). Many women do give up smoking in early pregnancy and do not consider themselves to have smoked during pregnancy when subsequently questioned. The question asked in this study could not separate out this group and this question should be addressed to exclude possible confounding.

PREMATURE BIRTH AND CHILDHOOD ASTHMA

While it is well established that children who survive bronchopulmonary dysplasia have poor airway function at school age, the long term outcome for pre-term infants who do not develop bronchopulmonary dysplasia has been little studied. This is particularly the case for pre-term infants who are born with birthweights of 2.5 kg or more. The analysis indicates pre-term but not low birthweight babies are at particular risk for developing childhood asthma.

Of pre-term babies born to asthmatic parents, almost half have been diagnosed as asthmatic at some time by a doctor. Asthma diagnosed by a doctor at some time could significantly overstate the current problem, thus a group of children with CWB were defined on the grounds that the occurrence of all three symptoms together was most likely to be asthma. This symptom triad is also significantly associated with having been born prematurely, although the absolute risk is about half the genetic risk from having asthmatic parents (Chapter 5/Kelly *et al* 1996).

The risk of asthma (doctor-diagnosed or CWB) was greater for premature babies. Babies born at full-term but who were less than 2.5 kg (i.e. small for gestational age (SGA)) were less likely than either full-term normal weight or pre-term babies to develop the symptom triad of CWB or have labelled asthma. This did not reach statistical significance and the percentage of asymptomatic children is similar to that in children born appropriate for gestational age. Nevertheless, this observation may be worth studying in a larger cohort. Could it be that growth retardation *in utero* in some way protects against asthma?

The relationship of prenatal and early postnatal events to lung function and airways responsiveness in schoolchildren has been studied prospectively for infants with birthweights less than 2000 grams (Chan and colleagues 1989a, 1989b). In these studies a reduction in airway function was observed in low birthweight children which was associated with cough but not wheeze. Other studies have shown that birthweight is related to lung size and methacholine responsiveness, and that prematurity and smoking during pregnancy appear to diminish airway size thus impairing lung function and increasing the likelihood of exercise-induced bronchospasm or of asthma diagnosis (Hanrahan *et al* 1992, Cunningham *et al* 1994, Demissie *et al* 1994b, Helms 1994, Stick *et al* 1996). A re-analysis controlling for confounding factors of the British National Birth Cohort of children born in one

week of 1970 confirmed the original observations of Golding and Butler implicating low birthweight in the aetiology of childhood wheezing (Lewis *et al* 1995).

The interrelationships of maternal asthma, active versus passive smoking by the parents, prematurity and birthweight have not been systematically studied. Thus if maternal asthma leads to prematurity and also influences the development of childhood asthma, it is likely that univariate analysis will show prematurity is associated with childhood asthma. The results show that prematurity remains important even when the parental asthma is controlled for and also that it is the prematurity that is relevant, regardless of birthweight.

The results also suggest that paternal smoking is not significant after adjusting for maternal smoking. This is probably because maternal and paternal smoking incidence is highly correlated. Thus passive smoking may be relatively unimportant, although this study was not designed to look at the effects of passive smoking and respiratory morbidity. Thus, objective measures of lung function or cigarette smoke exposure would be more sensitive in detecting an effect rather than questionnaire reporting of symptoms.

Chan *et al* (1989a, 1989b) have suggested a model of the aetiology of chronic respiratory morbidity in childhood based on birthweight, maternal smoking, genetic and environmental factors. They were unable to determine the relative importance of these factors because of the small size of their study. Analysis of more extensive data in the present study suggests that several different pathways are involved in the development of respiratory symptoms in childhood. Maternal asthma is associated with premature birth which is compounded if the mother smokes during pregnancy. Premature birth is associated with an increased risk of childhood wheezing, breathlessness and cough, whether or not the parents are asthmatic.

Maternal asthma is also associated with recurrent respiratory symptoms in children independently of whether the child is born pre-term. Early environmental exposures, during infancy or *in utero*, to allergens have also been implicated in the development of atopy and asthma (Peat *et al* 1990, Warner and Warner 1995). Thus it seems that there are several pathways by which asthma evolves.

The results indicate the importance of pre-term delivery in predisposing to respiratory symptoms in children. If this is confirmed then it should be possible to target particular groups of mothers or pre-term babies for intervention studies testing hypotheses related to causation. For example, premature babies of asthmatic mothers are at very high risk of childhood symptoms and would permit smaller longitudinal studies of asthma causation than would otherwise be possible. These are obvious target groups upon which to test the effectiveness of interventions in the future.

Chapter Eight

Methodology for case-control study

8.1 Study design

The objective of the case-control study was to determine whether there were quantitative differences in lung function, atopy and nutritional status between children with CWB or EC (case groups) and symptom free controls.

DEFINING CASES AND CONTROLS

Cases and controls were defined on the basis of questionnaire information from the 1993 dataset. Cases were defined as either having a history of CWB (n=61) or a history of EC (n=69), controls had no history of respiratory symptoms (n=148). Cases were matched by age (within six months), sex and consent to venepuncture with two controls.

8.2 Questionnaire

The questionnaire was completed by home interview with the child's parent or guardian. Questions relating to socio-economic factors included those about the presence of smokers in the household, damp or mould in the home, type of heating, fuel for cooking and pet ownership. Parents/guardians were asked about the mother's health during pregnancy, whether or not she smoked and a number of questions relating to the child's birth. Questions were asked about the respiratory health of parents, siblings and that of the study child. The presence of cough, wheeze and breathlessness were determined with the questions: "During the past year has your child had more cough, or got more coughs, than other children ?"; "Has your child had wheezing in the past year ?"; "During the past year has your child been breathless at rest or more breathless than expected after exercise ?" If the child had asthma questions about medication use and management were asked. The full questionnaire is shown in appendix C.

8.3 Anthropometry

Children were asked to remove shoes, socks and heavy clothing. Height was measured to the nearest millimetre using a Minimeter (Child Growth Foundation), weight was measured to the nearest 100 grams using electronic scales.

8.4 Lung function testing

Children were shown how to perform a forced expiratory manoeuvre in the standing position. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured using a dry bellows spirometer (Vitelograph, UK), peak expratory flow (PEF) was measured using a mini-Wright peak flow meter (Clement Clark, UK). After sufficient practice the highest of three measurements was recorded as baseline lung function. During field work predicted values for lung function were estimated using nomograms based on height, age and sex (Camprag 1977). Predicted values used in data analysis were calculated using the following regression equations (Rosenthal *et al* 1993).

FEV_1

Boys	<162.6 cm	-2.780 + 0.03425 x ht
	>162.5 cm	-5.108 + 0.05210 x ht
Girls	<152.6 cm	-2.734 + 0.03316 x ht
	>152.5 cm	-3.680 + 0.04112 x ht

FVC

Boys	<162.6 cm	-3.619 + 0.04129 x ht
	>162.5 cm	-7.038 + 0.06780 x ht
Girls	<152.6 cm	-3.311 + 0.03918 x ht
	>152.5 cm	-3.881 + 0.04512 x ht

PEF

Boys	<162.6 cm	-5.980 + 0.073 x ht
	>162.5 cm	-13.14 + 0.125 x ht
Girls	<152.6 cm	-6.790 + 0.079 x ht
	>152.5 cm	-3.940 + 0.064 x ht

Children were not asked to exercise if their baseline FEV_1 was less than 60% of the predicted value (Taussig *et al* 1980). A six minute standardised free running exercise test (groups of five children) was performed on the school playground or in the school gymnasium if weather conditions were unfavourable. Children were closely observed and actively encouraged to run as hard as they could. If a child became distressed the exercise test was stopped and the child rested. Nose-clips were not worn and asthma medication was taken as usual. FEV_1 measurements were taken at three, six and nine minutes after exercise (McQuitty and Lewiston 1982). If a child had a reduction of 15% or greater from baseline FEV_1 or a child had breathing difficulties a bronchodilater was given.

8.5 Skin testing

In order to determine whether or not a child was atopic, skin testing was performed. Children were asked to sit and rest their arms on a table surface. The volar surface of the lower arm was cleaned with an alcohol swab, the skin was marked at four centimetre intervals to indicate each test site. Drops of test solution containing allergen extracts for house dust mite, cat, dog, tree pollen, grass pollen, *Aspergillus*, feathers and the control solution histamine and physiological saline (Allergopharmia, Germany) were dropped onto the marked areas of skin. The skin was gently lifted at an oblique angle with a hypodermic needle. After 15 minutes the skin tests were read, each 'weal and flare' reaction was scored in the following way; weal absent and no erythema = 0, weal not greater than 1mm and erythema present = 1, weal up to 3mm with associated erythema = 2, weal between 3 and 5mm with erythema = 3, weal larger than 5mm or with pseudopodia = 4. Children washed their arms after the skin tests were read.

8.6 Blood analysis

Haemoglobin and zinc protoporphyrin were measured and used to indicate iron status. Vitamins A and E were measured in order to indicate serum antioxidant vitamin status. Vitamin E circulates in the low density lipoprotein portion of the blood and thus vitamin E status of the host is heavily influenced by the amount of circulating lipid. Cholesterol-adjusted vitamin E levels should be quoted to avoid missing vitamin E deficiency. A five ml blood sample was drawn by venopuncture by a doctor, 2.5ml were aliquoted into a washed glass tube, for whole blood analysis, and the remaining 2.5ml into an EDTA tube, for serum analysis. During field work samples were stored on ice inside a box for up to four hours. On return to the laboratory blood samples were prepared for various assays. Whole blood haemoglobin and zinc protoporphyrin were measured on the same day that samples were obtained. Samples for other assays were stored at -20 °C.

Haemoglobin (g/dl) (Hb) was assessed by the azidemethaemoglobin method using a HemoCue photmeter (HemoCue, Sweden). Zinc protoporphyrin (µmol/mol haem) (ZPP) was assessed using the ProtoFluor Reagent System (Helena Laboratories, UK). Serum vitamins A and E (µmol/l) (retinol and α-tocopherol) were measured by high performance liquid chromatography (Catignani and Bieri 1983). Normal serum levels for children were taken as; retinol 0.7-3.5 µmol/l and α-tocopherol 8.8-36.0 µmol/l (Farrel *et al* 1978, Gibson 1990, Forfar and Arneil 1992). Cholesterol and triglyceride (µmol/l) were measured using standard cholesterol II and triglyceride N assay kits (Wako Laboratories, UK).

Haemoglobin and ZPP were measured by the author, other assays were performed by a technician in the Tropical Medicine divisional laboratories at the School of Tropical Medicine, Liverpool.

8.7 Dietary assessment

Half of the surveyed children were chosen at random for further dietary assessment by the author and a dietician. Homes were visited and parents or guardians shown how to complete a three day dietary diary (Appendix D). The time of eating was logged, composition (with brand names if appropriate) and portion size were recorded. Participants were encouraged to record every food substance (meal, snack or confectionery) and any drink other than water. Three day records were kept for consecutive days (one weekend day and two week days). Homes were visited within one week and recorded entries checked with participants. Each foodstuff was coded according to McCance and Widdowson (1992) and Chan *et al* (1994). Food composition data were analysed using Microdiet (version 6.0) software which listed 33 macro and micronutrients, mean values of the three day dietary intake were used for analysis. Compliance with the full dietary assessment procedure was 87% (121/139), providing a sample of 121 for analysis.

8.8 Sample size

The sample size needed in each of two groups for a case-control study to have 90% confidence of estimating the population odds ratio to within 50% of the true value with an odds ratio of 2.0 when exposure to vitamin E deficiency among controls is estimated to be 20% was 60. It was estimated that there would be a 10% refusal rate to venopuncture during the field visits.

8.9 Study implementation

School visits were made over six weeks during May and June 1995 by the author, a physician and a school nurse. Anthropometry, lung function testing and skin testing measurements were recorded and a blood sample was taken during a day visit. Single re-visits were made for absentees. Home interviews and dietary assessments were arranged by telephone or letter,

these visits were completed between June and December 1995. Hb and ZPP were measured on the same day that blood samples were obtained, and the remaining assays were performed between June 1995 and May 1996.

The study was approved by the Paediatric Ethical Committee of The Royal Liverpool Children's Hospital, NHS Trust, Alder Hey.

8.10 Statistical analyses

The epidemiological package, Epi Info (version 6.0) was used. Matched pair analyses were performed for categorical variables, odds ratios and significance levels were calculated. For continuous variables analysis of variance or Kruscal-Wallis (for non-parametric data) tests were applied, p values were two tailed.

Chapter Nine

Assessment of antioxidant status - results in relation to respiratory symptoms

9.1 Introduction and objectives

Various hypotheses have been proposed to explain the rising prevalence of asthma in industrialised countries (Seaton *et al* 1994). Not all susceptible individuals who have a genetic predisposition will develop clinically significant disease and the spectrum of illness in symptomatic children ranges from chronic disability to mild symptoms of nocturnal cough. The nutritional status of the host has been hypothesised to influence this pattern of illness and Burney (1995) has proposed that 'it is surely not the hypothesis that lack of a particular nutrient is the cause of asthma; it is far more likely that lack of a nutrient would lead to a greater likelihood of asthma in a predisposed individual'. Dietary intakes and serum levels of the antioxidant vitamins A and C have been linked with reduced respiratory symptoms, improved lung function and reduced onset of obstructive lung disease in adults, but none of these studies have addressed the problem in children (Morabia *et al* 1989, 1990, Schwartz and Weiss 1990, Strachan *et al* 1991, Miedema *et al* 1993, Britton *et al* 1995, Troisi *et al* 1995).

Oxygen free radicals are products of natural oxidative processes which occur in all body tissues. Tissue damage in asthma is thought to be associated with the production of these reactive oxygen species during the inflammatory process (Barnes 1990). Vitamin E is a lipid soluble antioxidant which represents the principal defence against oxidant induced membrane injury (Heffner and Repine 1989). The biological activity of vitamin E is dependent not only on the dietary intake, but also on the availability of vitamin C which is needed to maintain the reduced form of vitamin E sequestered in cell membranes and other lipid structures (Packer *et al* 1979).

Children with an asthmatic predisposition, eating diets low in vitamin E and who are exposed to air pollutants which induce oxidative processes in the lung could be at particular risk of developing asthmatic symptoms. Inner city children who have been reported to have diets deficient in vitamin E (Doyle *et*

al 1994) and also to have a high prevalence of asthma (Brabin *et al* 1994/Chapter four) would be most likely to demonstrate this pathogenesis.

The objectives of this chapter were in children with different respiratory symptom profiles and asymptomatic controls to: (1) Determine the biochemical status of vitamins A and E. (2) Determine the dietary intake of antioxidant nutrients.

9.2 Methods

Subjects and methods were described in chapter eight. Cases had either a history of cough with wheeze and breathlessness (CWB) (n=61) or a history of excess cough as a solitary symptom (EC) (n=69). Cases were matched by age, sex and consent to venopuncture with two asymptomatic controls (n=148).

During a school visit anthropometric and lung function measurements were recorded and a blood sample was obtained. Serum levels of vitamins A and E and cholesterol were determined by assay methods. During a home visit a questionnaire was completed, questions asked included those about respiratory health and the home environmentl. In a sub-sample of children a three day dietary intake diary was completed (n=121).

A double matched analysis was performed for categorical variables odds ratios and 95% confidence intervals were calculated. For continuous variables analysis of variance and Kruscal-Wallis (for non-parametric data) tests were used, p values were two-tailed. Epi-info version 6.0 epidemiological package was used for analysis.

9.3 Results

Of the 278 children selected for the study 89.2% (248) consented to venepuncture, 85.3% (237) had exercise tests, 93.9% (261) had skin tests

and 231 (83.1%) had successful home interviews. Data were analysed for matched cases and controls who consented to venepuncture.

There were no differences in mean age (9.4 ± 1.3 years), height (133.9 ± 9.7 cm), weight (30.9 ± 7.2 kg), haemoglobin (12.3 ± 1.1 g/dl), cholesterol (4.2 ± 1.9 μmol/l) or triglyceride (1.2 ± 0.6 μmol/l) of children in the three groups. 53% (132) of the participants were boys.

Table 9.1 shows socio-economic data for cases and controls. Children with EC were more likely to live in rented accommodation and have an unemployed father than controls. The difference in socio-economic factors in children with EC and those with CWB were small.

Table 9.1 Socio-economic factors for cases and controls

	Controls (n=103)	EC (n=44)	CWB (n=43)
Smokers in household	59.2	48.8	52.3
Father unemployed	27.3	52.3$^{\cdot\cdot}$	43.2
Rented accommodation	28.9	50.0$^{\cdot}$	46.3
Damp or mould in home	13.6	27.9$^{\cdot}$	22.7

Analysis restricted to children for which a blood sample was obtained for whom questionnaire data was available. $^{\cdot}$ $p<0.05$, $^{\cdot\cdot}$ $p<0.01$ EC *vs* controls.

The proportions of children whose mothers were asthmatic was similar for those with CWB (20.8%) and EC (17.2%), but was much lower in controls (3.3%), table 9.2. There were no differences in mean resting or post-exercise lung function measurements between the three groups. Children with CWB were more likely to have a positive skin test compared to controls ($p=0.05$) and children with EC ($p=0.10$), and to have been taking anti-asthmatic medicine in the previous 12 months (both $p<0.001$).

Table 9.2 Respiratory characteristics of study groups

Variable	Controls (n=135)	EC (n=60)	CWB (n=57)
Maternal asthma, (%)*	4 (3.3)	10 (17.2)	11 (20.8)
Paternal asthma, (%)*	9 (7.5)	4 (6.9)	8 (15.1)
Parental asthma, (%)*	13 (10.8)	11 (19.0)	18 (34.0)
Anti-asthmatic medicines in previous 12 months, (%)*	4 (3.3)	9 (15.5)	35 (66.0)
Skin weal ≥3mm, (%)	27 (20.0)	13 (21.7)	19 (33.3)
FEV_1/FVC ratio, (SD)†	87.2 (6.4)	87.9 (4.5)	86.9 (6.6)
FEV_1 observed/predicted ratio, (SD)†	104.0 (13.8)	105.7 (17.2	101.2 (15.0)
FVC observed/predicted ratio, (SD)†	100.7 (13.8)	100.5 (14.8)	98.2 (14.4)
Post exercise drop of ≥15% FEV_1, (%)‡	16 (14.2)	9 (17.3)	10 (20.4)

FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; *Controls n=111, CWB n=49, EC n=49; †Controls n=114, CWB n=50, EC n=52; ‡Controls n=113, CWB n=49, EC n=52

Serum vitamins A and E levels

There was no effect of age or sex on serum levels of vitamins A and E. Table 9.3 shows mean serum vitamins A and E levels for cases and controls by family history of asthma. Mean serum vitamin E levels were significantly higher in the EC group compared to the CWB group for children with both a non-asthmatic and an asthmatic family history. Mean vitamin E levels were also significantly higher in children with EC than controls but only for those with an asthmatic family history. Comparable results were found for the vitamin E/cholesterol ratios (table 9.3). Using a level of 8.8 µmol/l of serum vitamin E as the lower limit of normal 13.9% (32/230) were vitamin E deficient. Vitamin E deficiency was significantly less common in the EC group (3.7%) than in either the controls (16.9%) ($p<0.01$) or the CWB group (17.3%) ($p=0.06$).

Table 9.3 Mean serum vitamin A and E and vitamin E / cholesterol ratio for cases and controls with and without a family history of asthma

	Non asthmatic			Significance level (p value)*		
	Controls (n=87)	EC (n=32)	CWB (n=27)	EC *vs* Control	CWB *vs* Control	CWB *vs* EC
Vitamin A, µmol/l	1.53	1.68	1.35	0.08	0.03	0.004
Vitamin E, µmol/l	14.85	17.44	13.50	0.07	0.64	0.02
Vitamin E / cholesterol ratio	3.77	4.60	3.54	0.04	0.61	0.03

	Asthmatic			Significance level (p value)*		
	Control (n=16)	EC (n=11)	CWB (n=17)	EC *vs* control	CWB *vs* control	CWB *vs* EC
Vitamin A, µmol/l	1.36	1.47	1.44	0.51	0.88	0.51
Vitamin E, µmol/l	11.99	18.62	13.18	0.007	0.56	0.03
Vitamin E / cholesterol ratio	3.05	4.68	3.42	0.02	0.55	0.07

* Analysis of variance or Kruscal-Wallis test for non-parametric data

Children with EC had higher mean serum retinol levels than controls or children with CWB. No child had vitamin A deficiency (<0.7 µmol/l). Children with EC (46.3%) and controls (29.0%) were more likely to have higher levels of serum retinol (>1.7 µmol/l) than children with CWB (15.4%), ($p<0.01$ and $p<0.05$ respectively). There was no difference in mean serum vitamin A and E for children who lived in a household with a smoker compared to those who did not.

Table 9.4 Dietary intakes of vitamins A, C, E, sodium and energy

Nutrient	Controls (n=65)	EC (n=28)	CWB (n=28)
Vitamin A, µg/day (SD)	833.4 (567.4)	764.1 (381.0)	690.0 (397.0)
Vitamin C, mg/day (SD)	81.6 (49.6)	70.0 (41.7)	61.4 (33.5)
Vitamin E, mg/day (SD)	4.6 (1.8)	4.3 (1.5)	3.7 (1.1)
Sodium, % RNI (SD)	249.0 (63.4)	224.0 (78.0)	219.0 (63.3)
Energy, kcal/day (SD)	2099.5 (452.0)	2022.9 (523.0)	1912.5 (423.0)

Dietary intakes

Dietary diaries were completed for 65 controls, 28 children with EC and 28 children with CWB. Table 9.4 shows the intakes of vitamins A, C and E and energy for cases and controls. Intakes of vitamins E and C were higher in controls than children with CWB, though not significantly when controlling for energy intake. There were no differences in vitamin A intakes between the three groups. The average consumption of vitamins A and C for all three groups was above recommended nutrient intakes (131% and 212% respectively). One child from the EC group was taking dietary supplements which included antioxidant vitamins. No published recommended intakes for vitamin E for children are available. There were no differences in intakes of 27 other nutrients between the groups. The correlation coefficient (r) between dietary intakes and serum levels was not significant for vitamin A ($r=0.06$) but

was close to statistical significance for vitamin E (r=0.18, 95% CI, -0.02 to +0.36, p=0.06). Sodium intakes were universally high, 249% of recommended nutrient intake in controls, 219% in the CWB group and 224% in children with EC.

9.4 Discussion

It is proposed that there may be two steps in the pathway to developing asthmatic respiratory symptoms in childhood. The first relates to the development of host susceptibility which may be linked to pre-term birth (Chapter seven/Kelly *et al* 1995), or genetic factors associated with atopy (Cookson *et al* 1992), or another factor yet to be defined. The second step relates to host antioxidant status with fewer respiratory symptoms occurring in susceptible children with better antioxidant status. To test this hypothesis children, living in an inner city area, at presumed risk of antioxidant vitamin deficiency and who were known to have a high prevalence of respiratory symptoms were selected. In this group of children the results showed that vitamin E deficiency is significantly less likely to be present in children with a history of milder respiratory symptoms, which may indicate mild asthma. This is the first time a case control approach defining different respiratory symptom categories in children, which may indicate mild and more severe forms of asthma, has been used to identify whether antioxidant vitamin status relates to disease profile.

These data are in keeping with a number of other studies of dietary or serum antioxidant vitamins in adults which have generally shown relatively weak beneficial effects of improved antioxidant status. Increased serum and dietary vitamin C intakes (often represented as fruit and fruit juice consumption) in adults have been associated with less wheezing and bronchitis, reduced incidence of lung disease and improved lung function (Schwartz and Weiss 1990, Strachan *et al* 1991, Miedema *et al* 1993). Serum

retinol and dietary intakes of vitamin A have also been proposed as predictors of lung function in adults (Morabia *et al* 1989, 1990). A recent report concluded that increased dietary intake of vitamin E may protect against adult onset asthma in women (Troisi *et al* 1995). Others have found no link between vitamin A intake and protection against obstructive lung disease in adults (Shahar *et al* 1994). In children only a single report has been identified from an industrialised area using a cross-sectional study design, which found no differences in serum tocopherol/cholesterol ratio, vitamin C or retinol in asthmatics compared to healthy controls (Powell *et al* 1994). However the data comprised a small group compared to the present study and results were not analysed by symptom severity and it is not clear if the children were living in a polluted area.

In the present study both dietary intakes and serum levels were measured and although there was no evidence of vitamin A deficiency, 16.9% of asymptomatic controls had biochemical evidence of vitamin E deficiency. A comparable prevalence of deficiency occurred in children with CWB (17.3%). Thus, children with CWB were exposed to the full consequence of the impaired nutritional state which was present in this community. In a population with adequate antioxidant status a linear relationship between respiratory symptom severity and serum antioxidant levels might be expected, with the highest vitamin E levels in asymptomatic controls and the lowest in the most severely affected asthmatics. Conversely, in a population with a high prevalence of vitamin E deficiency all children, including asymptomatic children would demonstrate vitamin E deficiency. In children predisposed to respiratory symptoms a selected group with milder symptoms (i.e. the EC group) should show improved vitamin E status compared to a more severely affected group (i.e. the CWB group) and controls who are not predisposed to respiratory symptoms. This is what was observed in this study and the conclusion is not that low levels of antioxidants cause asthma but that better

antioxidant status may protect susceptible children from developing more severe symptoms. Serum retinol levels also suggested that children in the EC group had better vitamin A status than children with CWB. These relationships were present for children who had asthmatic and non-asthmatic parents, and therefore may be important in susceptible children whether or not they have a genetic predisposition.

The concentration of total tocopherol in serum is the most frequently used biochemical index of vitamin E nutritional status, although its use as an index of vitamin E intake or status is questionable. Vitamin E is transported in serum mainly in LDL-lipoprotein fraction (Farrell *et al* 1978, Thurnham 1986). As blood lipid levels increase vitamin E is partitioned out of cell membranes and enters the circulation (Bieri *et al* 1977). Therefore vitamin E-cholesterol/lipid ratios should be quoted. We observed no difference in serum cholesterol or triglyceride levels between the study groups, and lipid adjusted values showed the same differences as mean serum vitamin E between cases and controls.

Children have lower levels of vitamin E than adults and it is not appropriate to use the adult range to assess vitamin E deficiency (Farrell *et al* 1978, Gibson 1990). In a study of inner city children in London, Doyle *et al* (1994) reported 38% at high risk of vitamin E deficiency, based on a cut-off of less than 15 µmol/l. If the same cut-off is applied to these data 54% of children would be defined as vitamin E deficient. Serum total tocopherol concentrations of less than 11.6 mol/l have been associated with greater than 5% haemolysis of red cells using the peroxide haemolysis test in adults (Gibson 1990). However, neither this or the higher cut-off used by Doyle *et al* are appropriate for paediatric populations. Many children have serum tocopherol less than 11.6 µmol/l due to low blood lipid concentrations but have no clinical or haematological evidence of vitamin E deficiency (Gibson 1990).

The three day estimated intake diary method was used for dietary assessment. This method has been shown to correlate closely with intake values estimated from weighed food intake methods, and is more accurate than 24 hour recall or food frequency questionnaires for the assessment of dietary intake (Bingham *et al* 1994). Dietary intakes of antioxidant vitamins were comparable for children in all three groups, except vitamin E intake which was lower in the CWB group. The high sodium intake observed reflects the large quantity of processed food which these children eat. The calculation for sodium intake in this study did not include any estimate for use of table salt and so these intakes are minimal values. Although more than twice the recommended nutrient intake for sodium was consumed by children, no difference in intake was observed between cases and controls. This is in contrast to other studies in adults which have reported increased sodium intakes in asthmatics (Burney 1987).

Endogenous reactive oxygen species and those from exogenous sources cause oxidative tissue damage if they accumulate. Animal studies have demonstrated the protective effects of vitamin E against oxidising air pollutants using vitamin E depleted animals (Menzel 1992), and it has been proposed that vitamin E can protect humans against the pathological effect of ozone in smog (Pyror 1991). Children in this Merseyside community are exposed to significant airborne dust pollution (Chapters four and six), which is a potential source of oxidants if oxidising substances are adsorbed on to the surface of particulates. It is plausible that vitamin E sufficiency could protect children from developing more severe respiratory symptoms due to the harmful effects of chronic exposure to airborne dust and other pollutants. Although vitamin A deficiency was not identified as a problem in cases or controls, the more optimal vitamin A status in the EC group compared to children with CWB should complement a protective effect of vitamin E.

The extent and public health significance of vitamin E deficiency should be assessed longitudinally, as it is not known whether this deficiency is chronic or seasonal. Assessment in pregnancy may also be important in view of the role of antioxidants in the pre-term lung (Fardy and Silverman 1995), and because asthmatic mothers have been shown to be at greater risk of delivering pre-term babies, who are in turn at greater risk of developing asthma (Chapter seven/Kelly *et al* 1995). Such babies could initially be at risk of developing asthma because of immature antioxidant enzyme systems (Fardy and Silverman 1995), or later because of diets with inadequate antioxidant content or because of a greater biochemical requirement. Improving their vitamin E status could be of value in reducing asthma symptom severity. Controlled intervention trials for different age groups are needed to determine the potential efficacy of vitamin E supplementation in reducing respiratory symptoms in children predisposed to asthma.

Chapter Ten

Assessment of antioxidant status - results in relation to lung function and exercise-induced bronchoconstriction

10.1 Introduction and objectives

It has been proposed that reductions in dietary consumption of antioxidants leads to reduced antioxidant defences in the lungs giving rise to increased susceptibility of populations to the potentially harmful effects of inhaled allergens and pollutants (Seaton *et al* 1994). Such an impairment of the lungs natural defence systems could be a contributory factor in the increasing prevalence of asthma over the past 30 years. This hypothesis is supported by observations of low asthma prevalence in rural communities in developing countries where highly processed 'Western' diets are not likely to be eaten (Godfrey *et al* 1975, van Niekerk *et al* 1979, Waite *et al* 1980, Keeley *et al* 1991, Addo Yobo *et al* 1997). Carey *et al* (1996) suggested a protective influence of Asian diet (which may be relatively unprocessed compared to an English diet) on wheeze and bronchial hyperreactivity in a study of school children in Leicester. Soutar *et al* (1997) reported that low dietary intake of vitamin C, magnesium and manganese were associated with increased risk of bronchial hyperresponsiveness (BHR) in adults.

It has been shown that antioxidant status is related to respiratory symptom severity in school children (Chapter nine). This leads to the hypothesis that serum antioxidant levels and dietary intake are related to lung function and BHR in children. If this hypothesis is correct the effects may be more readily detected in children than adults as their airways are rapidly developing and are immunologically immature.

The objectives of this analysis were to determine in children with and without exercise-induced bronchoconstriction (EIB): (1) biochemical antioxidant status, (2) dietary intake of antioxidants, (3) the relationship between lung function and serum antioxidant levels.

10.2 Methods

Subjects and methods for the case control study were described in chapter eight. Cases were defined as either having a history of cough with wheeze and breathlessness (CWB) (n=61) or excess cough as a solitary symptom (EC) (n=69). Asymptomatic controls were matched by age and sex.

During a school visit lung function; forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF) were recorded before and FEV_1 after a six minute free running exercise period. A positive exercise test was defined as a drop of 15% or more from baseline FEV_1. Skin testing to common aeroallergens was performed and a blood sample was obtained for biochemical nutritional status assessment.

A questionnaire on respiratory health and home environment was completed during a home visit with either the parent or guardian. A three day dietary diary was completed for a sub-sample of cases and controls.

Statistical analysis was performed using Epi-info. Significance testing was performed for categorical variables, analysis of variance and Kruscal-Wallis tests were used for continuous variables, p values were two-tailed. Linear regression analysis was used for correlations between indices of lung function and antioxidant vitamin levels in children with and without EIB.

10.3 Results

Questionnaire, lung function and biochemical data were available for 196 children, dietary data was available for 121 children. 15.3% (30/196) of children had a drop in FEV_1 of 15% or more from baseline FEV_1 after a six minute free running exercise period.

DEMOGRAPHIC AND SOCIAL FACTORS

Children with EIB were older than children without EIB (10.0 yrs *vs* 9.3 yrs, $p<0.01$). There was no difference between these groups in their mean

height or birthweight, the proportion born prematurely or breastfed and of mothers who smoked during pregnancy or at the time of the survey. A higher proportion of children without EIB lived in a household with a smoker, but this difference was not statistically significant (table 10.1).

RESPIRATORY FACTORS

There were no significant differences in the annual prevalence of cough, wheeze or breathlessness for children with EIB compared to those without. The proportion of children with and without EIB who were symptomatic is shown in table 10.2. For children with EIB the annual prevalence of wheeze and breathlessness was more common for boys (33.3% and 38.9%) compared to girls (16.7% and 16.7%) (p=0.4 and p=0.2, respectively) though not significantly. There was no difference in the annual prevalence of cough between boys and girls (38.9% *vs* 41.7%). No children with EIB had hayfever compared to 9.6% (16) of those without EIB (p=0.06). The presence of atopy (skin weal diameter 1mm or more than the saline control) was more common for children with EIB compared to those without (37.8% *vs* 27.3%, p=0.1). Atopy was more common among boys with or without EIB (table 10.2).

The proportion of children who had lost six or more days from school due to respiratory symptoms in the previous 12 months was higher for children with EIB compared to those without (16.7% *vs* 6.0%) but this difference was not statistically significant. There were no differences in resting lung function measurements for children with and without EIB (table 10.2).

Of the 30 children with EIB 16 (53%) were symptom free and 10 (33.3%) were taking asthma medication at the time of the survey. Of the 166 children without EIB 108 (65.1%) were symptom free, and the remaining 58 had the symptoms of cough, wheeze or breathlessness either singly or in

Table 10.1 Demographic and social characteristics of children with and without exercise induced bronchoconstriction

Variable	FEV, Drop <15%			FEV, Drop ≥ 15%		
	Boys (n=84)	*Girls (n=82)*	*Both sexes (n=166)*	*Boys (n=18)*	*Girls (n=12)*	*Both sexes (n=30)*
Age, yrs (SD)	9.5 (1.3)	9.1 (1.4)	9.3 (1.3)	9.9 (1.4)	10.2 (1.6)	10.0 (1.5)**
Height, cm (SD)	133.2 (9.9)	131.1 (11.0)	132.2 (10.1)	133.0 (7.9)	133.4 (10.8)	134.4 (9.1)
Birthweight, kg (SD)	3.42 (0.61)	3.16 (0.63)	3.29 (0.63)	3.42 (0.49)	3.19 (0.78)	3.33 (0.62)
Breastfed, %	40.5	36.6	38.6	33.3	50.0	40.0
Gestational age <37 wks, %	9.3	17.1	13.3	16.7	8.3	10.0
Smokers in household, %	63.1	59.8	61.4	55.6	33.3	46.7
Mother smoked during pregnancy, %	40.5	41.5	41.0	33.3	33.3	33.3
Mother current smoker, %	40.3	43.9	42.2	38.9	33.3	36.7

** P<0.01

Table 10.2 Respiratory indicators and lung function for children with and without exercise induced bronchoconstriction

	FEV_1 Drop <15%			FEV_1 Drop ≥ 15%		
Variable	*Boys (n=84)*	*Girls (n=82)*	*Both sexes (n=166)*	*Boys (n=18)*	*Girls (n=12)*	*Both sexes (n=30)*
Recent wheeze	20.2	17.1	18.7	33.3	16.7	26.7
Recent cough	35.7	29.3	32.5	38.9	41.7	40.0
Recent dyspnea	17.9	15.9	16.9	38.9	16.7	30.0
Recent asthma treatment	26.6	18.3	26.5	38.9	25.0	33.3
Respiratory illness aged < 2 yrs	26.2	30.5	28.3	33.3	25.0	30.0
Parental asthma	23.8	19.5	21.7	16.7	25.0	20.0
Hayfever	8.3	11.0	9.6	0	0	0
Eczema	22.6	28.0	25.3	22.2	8.3	16.7
Positive skin test, weal ≥1mm	33.3	21.2	27.3	45.5	26.7	37.8
Nocturnal cough	11.9	18.3	15.1	16.7	33.3	23.3
Cough after exercise	22.6	23.2	22.8	44.5	25.0	36.7
Colds go to the chest	47.6	43.1	46.4	27.5	58.3	40.0
School absence for ≥ 6 days in previous 12 months	6.0	11.0	8.4	16.7	16.7	16.7
FEV_1 % predicted (SD)	105.1 (13.8)	105.2 (17.2)	105.1 (15.6)	101.1 (11.3)	100.4 (13.4)	100.7 (12.0)
FVC % predicted (SD)	101.9 (12.5)	100.4 (16.2)	101.1 (14.4)	97.6 (11.5)	96.5 (15.2)	97.1 (13.0)
Resting FEV_1, l (SD)	1.89 (0.41)	1.78 (0.46)	1.83 (0.44)	1.9 (0.41)	1.8 (0.49)	1.86 (0.44)
Resting FVC, l (SD)	2.16 (0.46)	2.02 (0.52)	2.09 (0.50)	2.16 (0.47)	2.97 (0.56)	2.12 (0.50)
Resting PEF, l/min (SD)	301.2 (61.0)	287.0 (67.1)	294.1 (64.4)	281.5 (74.5)	281.3 (68.9)	281.5 (71.3)
Max. FEV_1 drop % of baseline	4.85 (5.6)	4.21 (6.1)	4.53 (5.9)	23.5 (9.2)	21.3 (6.0)	22.6 (8.1)

combination. Of these symptomatic children 33 (56.9%) were taking asthma medication. These children were more likely to be atopic (48.5% *vs* 12.0%, p<0.01), to have wheeze (72.7% *vs* 28.0%, p<0.001), breathlessness (69.7% *vs* 20.0%, p<0.001) and nocturnal cough (51.5% *vs* 28.0%, p=0.07), compared to the 25 symptomatic children not taking asthma treatment. For symptomatic children there were no significant differences in the proportions with a family history of asthma (30.3% *vs* 24.0%), respiratory illnesses when aged less than two years (51.5% *vs* 44.0%), hayfever (18.2% *vs* 8.0%), eczema (39.4% *vs* 36.0%) or cough after exercise (60.6% *vs* 44.0%) between those taking anti-asthma medication and those who were not. Neither was there any difference in the mean maximum percentage drop in FEV_1 from baseline after exercise in these children (4.70% ± 5.40 *vs* 4.74% ± 5.98).

Table 10.3 shows respiratory factors for children without EIB in relation to current asthma medication at the time of exercise testing. 34/166 children without EIB were taking mediation at the time of testing. Of those on medication one child was asymptomatic. The annual prevalences of cough, wheeze, breathlessness, a history of nocturnal cough (other than with a cold), cough after exercise, presence of atopy and school absence for six days or more due to respiratory symptoms were significantly more common for children who were taking asthma medication (all p<0.01). The prevalence of eczema and hayfever was higher for children taking asthma medication (38.2% *vs* 22.0%, p=0.05 and 17.6% *vs* 7.6%, p=0.08)). The difference in the prevalence of parental asthma between these groups (29.0% *vs* 19.7%) was not statistically significant.

ANTIOXIDANT STATUS

Table 10.4 shows serum antioxidant vitamin levels and dietary antioxidant intakes for children with and without EIB. Children with EIB consumed significantly less vitamin C than those without EIB (53.1 *vs* 69.6

Table 10.3 Prevalence of respiratory indicators for children without exercise induced bronchoconstriction

Variables	Asthma treatment		Significance level (p value)
	Yes (n=34)	No (n=132)	
Recent wheeze	70.6	5.3	<0.001
Recent cough	88.2	18.2	<0.001
Recent breathlessness	67.6	3.8	<0.001
Respiratory illness aged < 2 yrs	52.9	22.0	<0.001
Nocturnal cough	50.0	6.1	<0.001
Cough after exercise	58.8	13.6	<0.001
Colds go to the chest	88.2	35.6	<0.001
Hayfever	17.6	7.6	0.08
Eczema	38.2	22.0	0.05
Parental asthma	29.4	19.7	0.22
Positive skin test (weal > 1mm)	50.0	22.0	<0.01
School absence for ≥ 6 days in previous 12 months	32.4	2.3	<0.001
FEV_1 drop ≥ 10% after exercise	20.6	18.3	0.74

mg/day, p<0.05). There were no differences between these two groups in mean serum level of vitamins A and E or vitamin E/cholesterol ratio and dietary intakes of vitamins A and E, selenium, zinc, manganese, magnesium, sodium and energy.

Children with EIB and/or those taking asthma medication for whom dietary data were available were grouped together (n=36) and compared to children without EIB and not taking medication (n=85). Comparison of these groups showed no difference in the mean serum level of vitamin A (1.54 *vs* 1.49 μmol/l, p=0.66) or E (15.6 *vs* 14.7 μmol/l, p=0.66). Intake of vitamin A (587 *vs* 714 μg/day, p=0.1), C (55.8 *vs* 69.0 mg/day, p=0.09) and E (4.0 *vs* 4.4 mg/day, p=0.2) were lower for children with EIB and/or taking medication although not significantly. Neither were there any statistically significant differences in the dietary intakes of magnesium (206 *vs* 222 mg/day, p=0.66), selenium (36.3 *vs* 43.0 μg/day, p=0.14), zinc (6.9 *vs* 7.3 mg/day, p=0.5),

Table 10.4 Serum anti oxidant levels and dietary intakes for children with and without exercise induced bronchoconstriction. Values are mean (SD)

	FEV_1 Drop <15%			FEV_1 Drop ≥ 15%		
Variable	*Boys*	*Girls*	*Both sexes*	*Boys*	*Girls*	*Both sexes*
Serum	***(n=86)***	***(n=77)***	***(n=163)***	***(n=19)***	***(n=12)***	***(n=31)***
Vitamin E, µmol/l	15.4 (7.1)	15.1 (6.8)	15.3 (6.9)	16.2 (5.0)	16.6 (5.1)	16.4 (5.0)
Vitamin A, µmol/l	1.49 (0.41)	1.5 (0.39)	1.49 (0.40)	1.56 (0.31)	1.58 (0.44)	1.57 (0.36)
Vitamin E / cholesterol ratio	3.93 (1.90)	4.04 (2.02)	3.98 (1.95)	4.08 (1.93)	4.91 (2.00)	4.41 (1.97)
% vitamin E deficient, <8.8 µmol/l[†]	12.8 (86)	10.4 (77)	11.7 (163)	10.5 (19)	0 (12)	6.3 (31)
Diet	***(n=51)***	***(n=34)***	***(n=85)***	***(n=10)***	***(n=5)***	***(n=15)***
Vitamin E, mg/day	4.36 (1.5)	4.31 (1.8)	4.34 (1.6)	4.05 (1.9)	4.84 (1.4)	4.31 (1.8)
Vitamin A, µg/day	686.6 (403)	671.6 (499)	680.6 (441)	608.7 (298)	595.0 (217)	604.1 (264)
Vitamin C, mg/day	73.0 (45.5)	64.6 (36.4)	69.6 (42.1)	57.6 (51.5)	44.2 (20.0)	53.1 (43.1)[·]
Magnesium, mg/day	234.5 (99)	207.3 (60)	223.6 (87)	224.3 (137)	212.4 (65)	220.4 (115)
Manganese, mg/day	1.59 (0.7)	1.52 (0.6)	1.57 (0.7)	1.8 (1.0)	1.40 (0.9)	1.67 (1.0)
Selenium, µg/day	40.8 (27.6)	39.1 (16.4)	40.1 (23.6)	41.3 (24.4)	38.2 (15.6)	40.2 (21.3)
Zinc, mg/day	7.7 (2.9)	6.5 (2.3)	7.2 (2.7)	6.8 (2.6)	7.6 (2.9)	7.1 (3.2)
Sodium, mg/day	3069 (1185)	2901 (812)	3002 (1049)	3144 (1275)	2688 (761)	2991 (1122)
Energy, kcal/day	2105 (554)	1998 (304)	2063 (471)	2031 (559)	1976 (414)	2013 (501)

[†] values are % (number)

[·] $p<0.05$, Kruscal-Wallis test for non-parametric data

manganese (1.53 *vs* 1.58 mg/day, p=0.74), sodium (2801 *vs* 3070 mg/day, p=0.2) and energy (1950 *vs* 2076 kcal/day, p=0.17).

RELATIONSHIP BETWEEN SERUM ANTIOXIDANTS AND LUNG FUNCTION

Correlations between resting lung function (FEV_1 and PEF) and serum vitamin E in boys with different degrees of EIB are shown in figure 10.1. The correlations between FEV_1 and serum vitamin E for boys with a 10% (figure 10.1a), 15% (figure 10.1b) and 20% (figure 10.1c) drop in FEV_1 from baseline FEV_1 were significant ($p<0.05$, $p<0.01$ and $p<0.05$ respectively). Correlations between PEF and serum vitamin E for boys (figures 10.1d, 10.1e and 10.1f) were also positively associated but were less significant (p=0.06, p=0.05 and p=0.1 respectively). There were no significant correlations between resting lung function and serum vitamin E for girls. Figure 10.2 shows correlations between resting lung function (FEV_1 and FVC) and serum vitamin A in girls with different degrees of EIB. The correlations between FEV_1 and serum vitamin A for girls with a 10% (figure 10.2a) and 15% (figure 10.2b) drop in FEV_1 from baseline FEV_1 were significant ($p<0.001$ and $p<0.01$ respectively). Correlations between FVC and serum vitamin A (figure 10.2c and 10.2d) were also significant ($p<0.001$ and $p<0.01$ respectively). There were no significant correlations between resting lung function, EIB and serum vitamin A for boys.

MULTIVARIATE ANALYSIS

Tables 10.5 and 10.6 show partial F test statistics for the independent effects of serum levels of vitamins A and E on resting lung function, controlling for height, atopy, parental asthma, smokers at home and respiratory illnesses when aged less than two years. In boys serum vitamin E had significant independent effects on resting FEV_1 for those with a post exercise drop of 15% or more and on PEF for those with a 20% or more drop from baseline FEV_1, (table 10.5). In girls, vitamin A had a significant

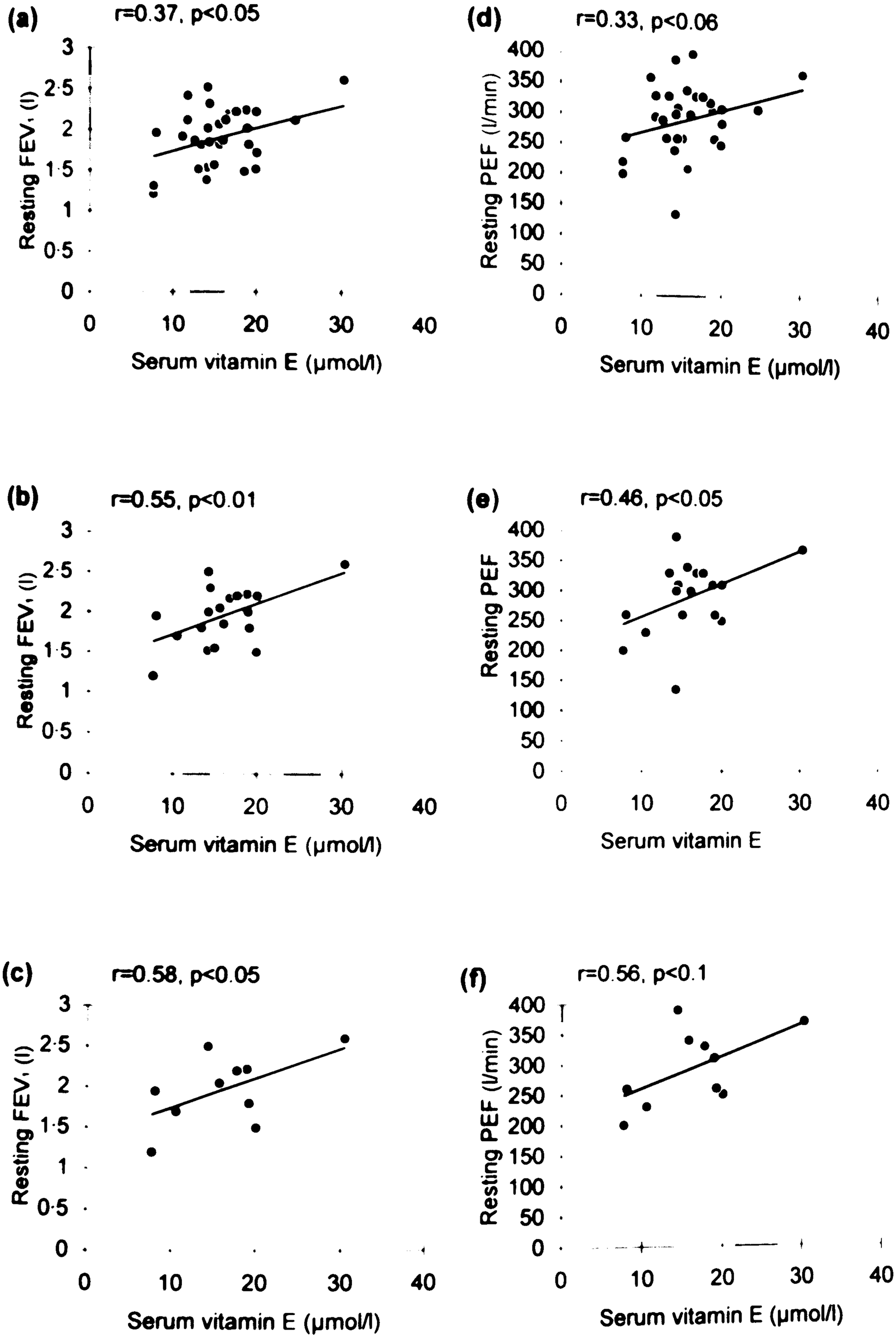


Figure 10.1 Correlations between serum vitamin E levels and resting lung function in boys. Drop ≥ 10% from baseline FEV_1, serum vitamin E vs resting (a) FEV_1 and (d) PEF. Drop ≥ 15% from baseline FEV_1, serum vitamin E vs resting (b) FEV_1 and (e) PEF. Drop ≥ 20% from baseline FEV_1, serum vitamin E vs resting (c) FEV_1 and (f) PEF.

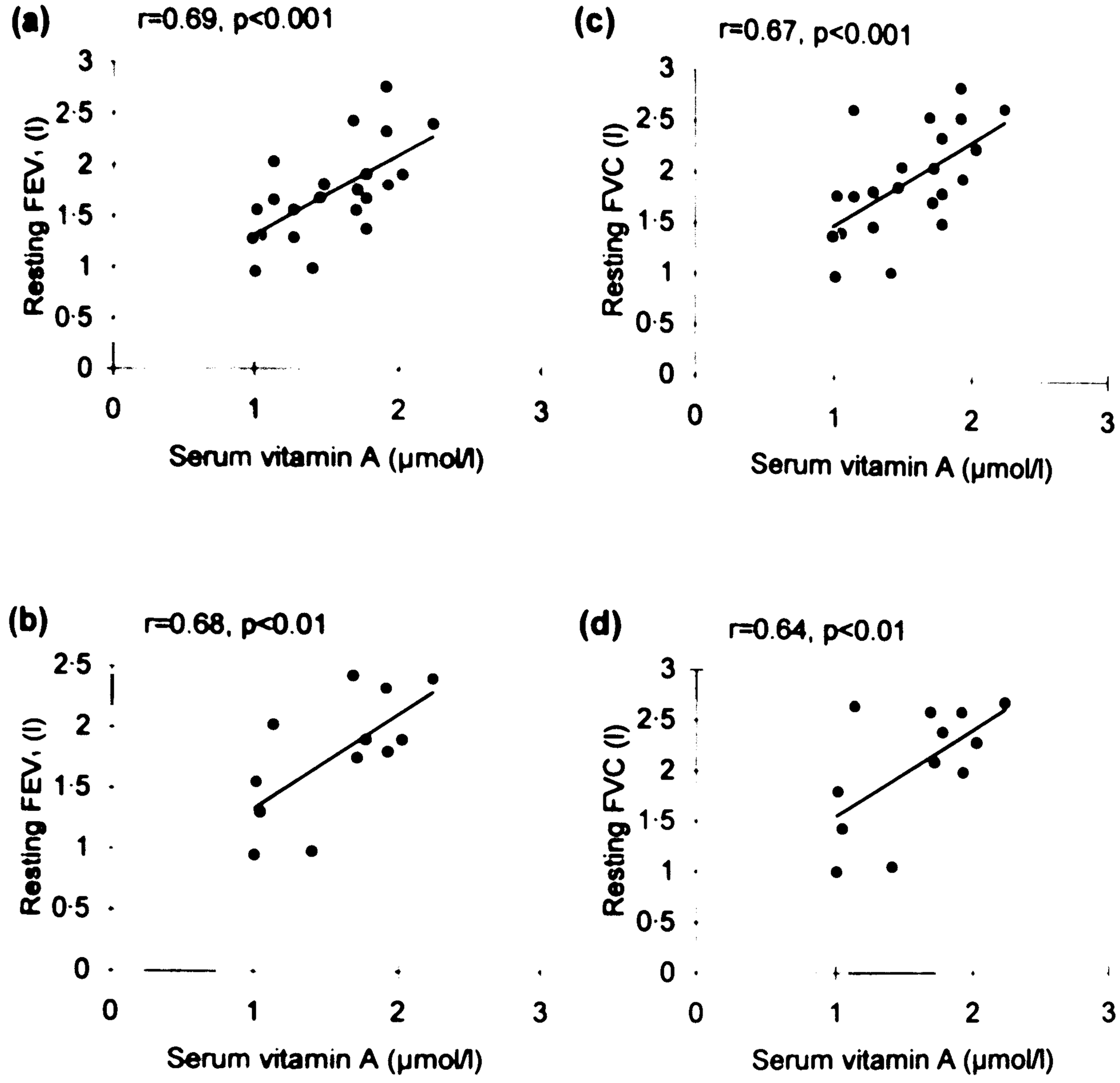


Figure 10.2 Correlations between serum vitamin A levels and resting lung function in girls. Drop ≥ 10% from baseline FEV_1, serum vitamin A vs resting lung function (a) FEV_1 and (c) FVC. Drop ≥ 15% from baseline FEV_1, serum vitamin A vs resting lung function (b) FEV_1 and (d) FVC.

Table 10.5 Multiple linear regression analysis shows the relationship between serum vitamin E level and resting lung function in boys controlling for height, family history of asthma, atopy, smokers in the household and respiratory illness when aged < 2 years. Values are partial F statistics

	Index of lung function	
% drop from baseline FEV_1	*FEV_1*	*PEF*
≥10	0.80	1.5
≥15	11.1**	1.4
≥20	2.7	5.8*

* p<0.05, ** p<0.01

Table 10.6 Multiple linear regression analysis shows the relationship between serum vitamin A level and resting lung function in girls controlling for height, family history of asthma, atopy, smokers in the household and respiratory illness when aged < 2 years. Values are partial F statistics

	Index of lung function	
% drop from baseline FEV_1	*FEV_1*	*FVC*
≥10	10.7**	8.7**
≥15	7.6**	4.3*

* p<0.05, ** p<0.01

independent effect on resting FEV_1 and FVC for those with post-exercise drops of 10% and 15% from baseline FEV_1 (table 10.6).

10.4 Discussion

METHODOLOGICAL ISSUES

Protocols for exercise testing are difficult to apply in the community setting. In the laboratory it is possible to control the temperature and humidity of the inspired air which is known to influence the occurrence of exercise induced bronchoconstriction. In field studies relative humidity can be recorded, which if above 10 mg H_2O/l is considered to reduce the sensitivity of the test (Hahn *et al* 1984). In the laboratory direct estimates of oxygen consumption are easier to measure, though indirectly if distance run and heart

rate are recorded oxygen consumption can be estimated (Silverman and Anderson 1972b). Laboratory studies often use well defined 'asthmatic' and 'normal' individuals for study (Mellis *et al* 1978, Godfrey *et al* 1991) whereas heterogeneous populations are often used in epidemiological investigations.

Exercise testing protocols have been widely used in epidemiological studies either to screen for undetected asthma, determine asthma prevalence or to characterise more thoroughly children with predetermined symptomatology (Burr *et al* 1989a, Clough *et al* 1991, Williams *et al* 1993). However, methods used such as type of exercise, index of lung function, drop from baseline reading and timing of post exercise measurements vary between studies and so make them difficult to compare. Haby and colleagues (1994) have suggested that if the same protocol were followed for exercise testing in field studies results would be reliable, accurate and could be an alternative to widely used pharmacologic challenges.

In this study forced expiratory volume in one second (FEV_1) was used to assess lung function. This has been reported to be more reproducible than PEF (Cropp *et al* 1975, Strachan 1989b) and has been widely used by others (Kattan *et al* 1978, Barry *et al* 1991, Clough *et al* 1991, Godfrey *et al* 1991, Ninan and Russell 1993, Haby *et al* 1994, Ponsonby *et al* 1996, Powell *et al* 1996, West *et al* 1996). The percentage drop from baseline lung function which is used to define EIB varies widely between studies. Some investigators have calculated the normal range of post exercise lung function in their own populations in order to detect unrecognised asthma. Such calculations have given reductions from baseline lung function between 10 and 21% to indicate BHR (Kattan *et al* 1978, Frischer *et al* 1993b, Haby *et al* 1994, Busquets *et al* 1996, Ponsonby *et al* 1996, Powell *et al* 1996, Addo Yobo *et al* 1997). Arbitrary cut offs of 10% and 15% reduction in lung function have been commonly used to define EIB (Burr *et al* 1974 and 1989a, Tsankaras *et al* 1988, Barry *et al* 1991, Clough *et al* 1991, Keeley *et al* 1991, Bardagi *et al*

1993, Ninan and Russell 1993, Williams *et al* 1993, Agudo *et al* 1994, Austin *et al* 1994, Nichols and Longsworth 1995, West *et al* 1996). In this study an arbitrary cut-off of 15% drop from baseline FEV_1 was used to define EIB. If the mean drop in FEV_1 of 'normal' children plus 1.96 times the standard deviation in post-exercise FEV_1 were taken the maximum acceptable drop within the 'normal' population would be 15.8% and thus within the range calculated by other workers. The timing of post-exercise measurements is another variable feature of exercise protocols, we measured FEV_1 at 3, 6 and 9 minutes which has been used by others (Frischer *et al* 1993b).

The type of exercise used is important, free running for six minutes has been shown to be the most provocative for BHR to exercise (Silverman and Anderson 1972a, Godfrey *et al* 1973) and has been widely used (Tsankars *et al* 1988, Burr *et al* 1989a, Barry *et al* 1991, Haby *et al* 1994, Addo Yobo *et al* 1997). The bicycle ergometer has also been used to test for EIB (Ninan and Russell 1993, von Mutius *et al* 1994, Nichols and Longsworth 1995, West *et al* 1996). In order to ensure maximal effort, heart rate (85-90% predicted maximum) oxygen consumption and the distance ran, can be measured (Silverman and Anderson 1972b). Sub-maximal heart rate has been shown to be attained within six minutes of exercise (Tsankaras *et al* 1988). Powell *et al* (1996b) reported that 95% of children had sub-maximal heart rates at the end of six minutes, and it has been shown that 90% of children reach this level of exercise intensity within the first minute of exercise (Haby *et al* 1994). We did not monitor heart rate but children were closely observed and actively encouraged to work as hard as they could, therefore with evidence from other studies we are confident that the majority of children easily complied with the required exercise intensity. It is possible that not measuring exercise intensity may have reduced the sensitivity of our test, although this limitation is apparent in other studies (Burr *et al* 1974 and 1989a, Barry *et al* 1991, Keeley *et al* 1991). The use of nose clips to ensure mouth breathing could

theoretically help to maximise exercise stimulus (Haby *et al* 1994). We did not use nose clips as potential discomfort may have affected compliance. Testing was performed on the school playground on 13 occasions and indoors twice due to inclement weather conditions, relative humidity was below 10 mg H_2O/l on each of our test days. A standardised protocol for exercise testing in the epidemiological context is important if studies are to be comparable. Such protocols could include standardisation of exercise intensity, accurate recording of ambient air conditions and wearing of nose clips to ensure mouth breathing, though such measures would be more labour intensive and may restrict the numbers of children studied.

We did not interfere with the children's asthma treatment regimens which is an approach which has been used by others (Tsankaras *et al* 1988, Frischer *et al* 1993b, Williams *et al* 1993, Powell *et al* 1996). Therefore it was not appropriate to calculate the sensitivity of the testing method as 57% of known symptomatic children were taking asthma medication, however 22% of children receiving treatment had a positive exercise test which suggests that their medication may have been sub-optimal. Tsankaras and colleagues (1988) reported that half of the known asthmatics in their study did not have a positive exercise test, which the authors concluded reflected good quality of asthma care.

Powell and colleagues (1996) reported that exercise testing had poor within individual reproducibility in community based school populations. The variable nature of BHR over short periods of time has also been reported in relation to responses to pharmacologic challenge in children (Josephs *et al* 1989, Clough *et al* 1991). Studies which have compared exercise and inhalation challenges do not always identify the same individuals and thus show poor correlation. Such observations support the hypothesis that different provocation tests identify different airway abnormalities (Bhagat and

Grunstein 1984, Foresi *et al* 1986, Fourie and Joubert 1988, Clough *et al* 1991, Haby *et al* 1994).

Agudo *et al* (1994) reported that children exposed to tobacco smoke from their mothers were at increased risk of having EIB than those not exposed to ETS. In the present study there were no differences in socio-economic characteristics of children with and without EIB. Frischer *et al* (1993b) and Addo Yobo *et al* (1997) have reported that positive exercise tests are associated with atopy, assessed by skin testing. In the present study there was evidence of atopy in 27% of children with a negative exercise test. This was in part due to positive skin tests in those with well controlled asthma. Of asymptomatic children with a negative exercise test 22%, had a positive skin test compared to 38% of children with EIB. A third of all children with EIB were receiving asthma treatment and children with a positive exercise test were also more likely to have lost six days or more from school due to respiratory symptoms. This suggests that their asthma was not well controlled.

NUTRITION AND LUNG FUNCTION

Evidence for a beneficial effect of dietary antioxidants on respiratory health is based mainly on studies in adults. Increased consumption of fresh fruit and vegetables and vitamin C have been associated with better lung function and to have an independent effect on lung function (Strachan *et al* 1991, Britton *et al* 1995). Morabia and colleagues (1989, 1990) reported that dietary intake and serum levels of vitamin A were predictors of lung function. Powell *et al* (1994) reported reduction of the antioxidant enzyme, red cell glutathione peroxidase activity in asthmatic children compared to controls, but no difference in levels of vitamins A, C and E. Selenium which is an important co-factor for glutathione peroxidase activity has been shown to be reduced in asthmatics (Stone *et al* 1989, Platt *et al* 1990). Studies from Nigeria (Anah *et al* 1980, Aderelle *et al* 1985) have suggested that administration of large

doses of vitamin C in adults and children may be related to less severe asthma. Vitamin C administration has been shown to reduce bronchoconstriction due to the inhalation of nitrogen dioxide, ozone and BHR to methacholine and histamine (Zuskin *et al* 1975, Mohsenin and colleagues 1983, 1987, Chatham *et al* 1987). Carey *et al* (1996) reported that children consuming an Asian diet, which may be less processed, were less likely to have BHR to methacholine than children taking an English diet. Soutar *et al* (1997) showed no difference in antioxidant intake between adults with and without seasonal rhinitis, but showed significantly lower intakes of vitamin C, manganese and magnesium, higher fat and lower fibre in those with BHR to methacholine. The present study showed that vitamin C intake was reduced in children with EIB. There were no differences in the intakes of vitamins A and E, selenium, manganese, magnesium or zinc in children with and without EIB, nor were there any differences in mean serum levels of vitamins A and E.

There are several proposed mechanisms by which vitamin C may ameliorate bronchial hyperresponsiveness, these include: The reduction of the biosynthesis of the smooth muscle constrictor prostaglandin $PGF_{2\alpha}$ in favour of the dilator $PGE_{2\alpha}$, the promotion of non-enzymatic degradation of histamine, to decrease smooth muscle contractility and to help maintain the lung redox state (Bucco *et al* 1992).

There are sex differences in the occurrence of wheezing illness in children, in the first decade of life boys are more likely to develop asthma than girls (Horswood *et al* 1985, Ownby 1990, Martinez *et al* 1991). There were no difference in the dietary intake of antioxidants between the sexes. No other studies were identified that reported sex differences in the effects of antioxidant status on disease occurrence, lung function or BHR in children. The present study demonstrated sex differences in correlations between indices of resting lung function and serum vitamin levels in children with arbitrarily defined EIB. In girls with a significant post-exercise drop in lung

function, resting FEV_1 and FVC were related to serum levels of vitamin A. In boys a similar pattern was demonstrated in those with EIB whose resting FEV_1 was associated with serum levels of vitamin E. It is not clear why different antioxidant vitamins should correlate with resting lung function in girls and boys separately. These associations require further investigation.

Thus, antioxidants in the diet may have important influences on lung function in children. Improving diet or supplementing that of high risk groups may contribute to the prevention of disease, reduce symptom severity or bronchoconstriction to physical or chemical stimuli. The results of this analysis indicate that serum levels of vitamins E and A are related to lung function in children.

It is uncertain whether these associations are acute or chronic or whether seasonal variations in dietary intakes and antioxidant status may influence bronchial hyperresponsiveness at different times of the year. Further studies are required to ascertain the duration of these associations in individual children in order to determine whether there is a scientific basis for antioxidant supplementation studies in children with asthma.

Chapter Eleven

Overview

11.1 Respiratory morbidity in an area of increased dust pollution

The results of the first cross-sectional survey showed that there was increased respiratory morbidity in school children in the dust exposed area compared to children in control areas. This was manifested by increased parental reporting of excess cough and time off school due to respiratory symptoms, although there was no difference in hospital admissions due to respiratory symptoms. Lung function measurements were within the normal range, although recordings were taken when the children were in school and therefore well. A spatial relationship between symptoms and proximity to the coal stockpiles was shown (unpublished findings), this indicated that the source of the dust was in the dock area. These observations suggest that for children with excess cough, in the dust exposed area, that the symptom is of nuisance value rather than being life threatening. However, it is important not to over-interpret these results as cross-sectional studies cannot attribute cause and effect.

Exposure to increased levels of coal dust, e.g. surface coal workers, does not result in long-term effects on respiratory health. However the lungs of young children are structurally and immunologically immature and it is possible that their lungs handle inhaled dust differentially compared to adults.

11.2 What condition do the symptoms represent ?

It was not clear whether the symptom of excess cough represented an irritant response related to an increased dust burden, or whether it represented asthma. Comparisons of asthma prevalence between studies is difficult if the definition of asthma used in surveys differs. The prevalence of reported doctor diagnosed asthma is influenced by a number of factors including the diagnostic preference of the physician and parental recall.

The prevalence of doctor diagnosed asthma in this Merseyside community was roughly 20%, In order to estimate the true prevalence of

asthma the children were subdivided on the basis of their respiratory symptoms. The symptom triad of cough with wheeze and breathlessness (CWB) was proposed as a better questionnaire definition of asthma than reporting of single symptoms or doctor diagnosed asthma. It was shown that the risk factors associated with CWB were related to predisposition such as maternal asthma, history of allergies and pre-term birth. Whereas, EC was associated with adverse environmental factors such as attending school in an area of increased dust pollution and damp in the home. It was concluded that CWB may be a better marker of childhood asthma in epidemiological surveys than reporting of single symptoms or doctor diagnosed asthma.

EC was more common in younger children (aged four and five) and appeared to be transitory, with over half of the children recovering within two years. As the age specific prevalence of EC falls with increasing age the occurrence of this symptom may be related to the number of respiratory infections and/or relatively greater irritant effect of dust in smaller airways. In contrast, the age specific prevalence of the symptom triad CWB did not fluctuate and this symptom combination appeared to be persistent showing low recovery rates. These observations support the hypothesis that EC may be less clinically significant than CWB or 'asthma'.

11.3 Temporal effects

Two years after the first cross-sectional survey a second survey was performed in the same 15 primary schools using the same methodology. This allowed the results of the 1993 survey to be directly compared with those from the 1991 study. Improved environmental protection measures had been implemented in the Bootle Dock area leading to reductions in dust levels, although levels were still four times higher than those in control areas. There were no changes in the prevalence of excess cough or school absenteeism due to respiratory symptoms in the exposed area, however the prevalence of

CWB fell by 4.4%. In control areas there were increases in the prevalence of respiratory symptoms, prescribed asthma treatment, school absences and hospital admissions due to respiratory symptoms and increased symptom severity between the surveys. Despite these changes the prevalence of excess cough and school absenteeism remained higher in the exposed compared to the control areas

The observations indicate that if dust levels are related to the prevalence of EC, further reductions in dust levels are required in order to achieve a lower prevalence of EC in the exposed area.

11.4 Maternal asthma and prematurity

The assessment of the impact of maternal asthma on pre-term birth and the subsequent development of respiratory symptoms later in childhood was not an *apriori* objective of this work, therefore these observations can be regarded as incidental.

The analysis separated out the effects of prematurity and being born small for gestational age on the risk of developing respiratory symptoms later in childhood. It was shown that premature birth was associated with an increased risk of childhood CWB whether or not there was a family history of asthma. The magnitude of this risk was about half that associated with the child's mother having asthma. A weak association between babies who were born small for dates and reduced risk of having CWB or diagnosed asthma was also observed. It was shown that the prevalence of pre-term delivery was highest in asthmatic women who smoked during pregnancy and lowest in non-asthmatic, non-smoking women. Maternal asthma and smoking during pregnancy had significant independent effects on the risk of pre-term delivery, thus the effect of maternal asthma appears to be compounded by the effect of smoking during pregnancy. Further studies are needed in order to determine

whether paternal smoking is associated with an increased risk of pre-term birth.

11.5 Antioxidant nutritional status, respiratory symptoms and lung function

For the case-control study children were selected on the basis of information collected in the 1993 survey. Children had either a history of CWB (which was proposed as a surrogate for childhood asthma) or EC (which was related to environmental conditions and residential proximity to the dock, and may represent mild respiratory disease), or were symptom-free.

When nutritional factors were examined significant differences between these groups of children with different respiratory symptom profiles were observed.

The study population was largely from an inner city area and were considered to be at risk of both poor nutrition as well as the effects of exogenous oxidative damage from air pollutants. It was proposed that the antioxidant nutritional status of children with different respiratory symptoms would differ, with those children with better antioxidant status experiencing fewer symptoms.

Mean serum antioxidant vitamin (A and E) levels were higher in children with EC compared to controls and children with CWB, whether or not they had a family history of asthma. Biochemical vitamin E deficiency (<8.8 μmol/l) was common, affecting 16.9% of asymptomatic controls. Vitamin E deficiency was significantly less likely to occur in children with a history of EC compared to symptom-free controls and children with CWB. There were no significant differences in dietary intakes of vitamins A, C and E in children with respiratory symptoms and controls, although children with CWB consumed less vitamin E compared to other children. Nutritional status was assessed on only one occasion and therefore in order to determine whether vitamin E

deficiency in these children is acute or chronic longitudinal studies are required.

The hypothesis that serum antioxidant levels are related to lung function and bronchial hyperrespnsiveness was also tested. There were no differences in serum antioxidant status between children with and without exercise induced bronchoconstriction (EIB). When the dietary intakes of these children were examined it was shown children with EIB had lower intakes of vitamin C compared to those without EIB. Reduced vitamin C intake has been shown by others to be associated with increased bronchial reactivity. Mechanisms by which vitamin C may reduce bronchial reactivity include: reduction of constrictor prostaglandin synthesis and promoting the non-enzymatic degradation of histamine. Sex differences were observed in linear correlations between indices of lung function and serum antioxidant levels. In girls with EIB resting lung function was significantly correlated with serum levels of vitamin A. Resting lung function in boys with EIB was significantly correlated with serum levels of vitamin E. It is not clear why these sex differences occur. This observation requires further study in a larger sample of children as it may be related to the low statistical power of this study.

The beneficial effects of improving antioxidant status on respiratory health have been shown largely in studies on adults, and stronger associations may be observed in children.

11.6 Implications for further work

In studies performed so far pollution monitoring has been based on levels of total dust. Measurements of PM_{10}, NO_2, SO_2 and O_3 are now available in the Sefton area (personal communication with Dr John Reid, Sefton Health). Quantitative and qualitative data on dust and other pollutants in the area will help to determine whether it is particle size or composition that

is associated with respiratory symptoms. Monitoring of children's respiratory health in Merseyside in relation to pollution levels should include:

i Repeat cross-sectional questionnaire based surveys of respiratory health in primary school children, in order to determine whether pollution levels and symptom prevalence are falling. Some of the core questions from the ISAAC questionnaire should be included in order to make comparisons with other studies.

ii Panel or event studies in asthmatic and non-asthmatic children in order to determine whether fluctuations in pollution levels are related to reported respiratory symptoms, lung function, school absenteeism, inhaler usage, general practice attendance or hospital admissions.

iii Longitudinal follow-up of the 1991 cohort to determine whether symptoms reported in childhood have persisted into adolescence.

iv Measurement of salivary cotinine in selected groups of children in order to quantify exposure to environmental tobacco smoke in relation to respiratory symptoms and lung function.

The effects of maternal smoking during pregnancy on the respiratory health of the child are avoidable. If children start life at a disadvantage the effects may continue throughout life and their disabilities may impart a considerable burden on society. Studies on effects of maternal factors and pre-term birth should include:

v A higher priority should be given to health education programmes aimed at pregnant women concerning the risks of smoking during pregnancy.

vi. Monitoring of maternal asthma prevalence and primary care.

vii Recruitment of pregnant asthmatic women, to examine the impact of maternal asthma on the gestational age of their babies.

viii Longitudinal follow-up of pre-term babies to evaluate whether they are at increased risk of respiratory symptoms during infancy and childhood.

ix Follow-up of babies born small for gestational age in order to determine whether they are at reduced risk of respiratory morbidity in childhood compared to babies born with weights appropriate for gestational age.

Improving antioxidant vitamin status could be of value in reducing respiratory symptom severity. Further studies are needed in order to determine the scientific basis for controlled intervention trials. This would involve evaluating the efficacy of antioxidant supplementation in reducing symptom severity. Priority should be given to the following studies:

x Longitudinal follow-up of children with vitamin E deficiency in order to determine whether it is acute or chronic.

xi Assessment of antioxidant status in children attending asthma clinics.

xii Cross-cultural assessment of antioxidant status, enzyme activity and functional measures of lipid peroxidation in a large sample of children consuming different diets, in relation to respiratory symptoms, lung function and bronchial hyperreactivity.

Could our grandparents' impression that cod liver oil is beneficial for child health be correct after all ?

Chapter Twelve

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Appendix A

Questionnaire used in cross-sectional and longitudinal surveys

SOUTH SEFTON HEALTH AUTHORITY
AND WIRRAL AREA HEALTH AUTHORITY

CHILDREN'S QUESTIONNAIRE

IMPORTANT : Before completing this questionnaire please give the following details:

Child's Name : _ Class _ _ _ _ _

Home address: _

_ _

_ _

Postcode: _ _ _ _ _ _ _ _

Home telephone No: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

School: _

These questions can be answered by ticking the best answer or by filling in the blank

Example : Do you live in England? 1 ☑ YES 2 ☐ NO

Child's age: ☐☐ Years ☐☐ Months

Sex: 1 ☐ Boy 2 ☐ Girl

How long has your child been attending this school?

☐☐ Years ☐☐ Months

Has your child been resident at your present address for 3 years?

☐ YES ☐ NO

If NO what has been your residential address in the last 3 years ?
Please give postcode.

_ _

_ _

_ _

PART A GENERAL

1. Has your child ever been diagnosed by a doctor as having asthma or bronchial asthma ? 1 ☐ YES 2 ☐ NO

2. For what length of time did your child exhibit symtoms of Asthma before he/she was diagnosed by a doctor? ☐☐ MONTHS

3. If your child has Asthma do you consider it is well controlled? 1 ☐ YES 2 ☐ NO

4. Do you consider your child to be healthy ? 1 ☐ YES 2 ☐ NO

   If no why not ? _

5. Has your child ever been diagnosed by a doctor as having bronchitis? 1 ☐ YES 2 ☐ NO

6. Has your child ever been diagnosed by a doctor as having croup? 1 ☐ YES 2 ☐ NO

7. Does your child have any allergies ? 1 ☐ YES 2 ☐ NO
   Hayfever 1 ☐ YES 2 ☐ NO
   Eczema 1 ☐ YES 2 ☐ NO

8. Has your child ever had any other health problems ? 1 ☐ YES 2 ☐ NO
   If "YES" please specify

   _____

   _____

9. How many smokers are there in your household (smoking at least 1 cigarette per day)

   Cigarette smokers ☐

   Pipe smokers ☐

10. Do you have a family pet or owned one within the past 3 years?

	At present 1	At present 2	Previously 1	Previously 2
Cat	☐ YES	☐ NO	☐ YES	☐ NO
Dog	☐ YES	☐ NO	☐ YES	☐ NO
Bird	☐ YES	☐ NO	☐ YES	☐ NO
Other	☐ YES	☐ NO	☐ YES	☐ NO

A continued

11. To build up a complete picture of the health of all children it is important to know exactly as possible the occupation at present of each parent. (If never in employment please state none).

MOTHER _____

FATHER _____

12. Last occupation of parent ?

MOTHER _____

FATHER _____

13. Are you presently in paid employment ?

	1		2	
MOTHER	☐	YES	☐	NO
FATHER	☐	YES	☐	NO

14. Do you work in a dusty environment ?

	1		2	
MOTHER	☐	YES	☐	NO
FATHER	☐	YES	☐	NO

15. Do you own your home? 1 ☐

Pay a mortgage? 2 ☐

Rent your home? 3 ☐

16. What was the birth weight of your child?

_____

17. Was your baby born prematurely?

1		2	
☐	YES	☐	NO

18. Did you breastfeed your baby ?

1		2	
☐	YES	☐	NO

19. For what length of time did you breastfeed your baby ?

☐☐ MONTHS

20 . Is your child taking any medicine at present ?

1		2	
☐	YES	☐	NO

IF " YES " COPY FROM THE LABEL ON THE MEDICINE, THE FOLLOWING DETAILS

	NAME OF DRUG	HOW OFTEN PER DAY	NUMBER OF TABLETS PER DAY	NO. OF PUFFS
a				
b				
c				
d				
e				
f				
g				
h				

21. Does the child's father or mother suffer from Asthma ? (diagnosed by a doctor)

	1		2	
Father	☐	YES	☐	NO
Mother	☐	YES	☐	NO

22. What is the main method of heating in your living room?

	1		2	
Coal fire	☐	YES	☐	NO
Electric units	☐	YES	☐	NO
Gas units	☐	YES	☐	NO
Central heating	☐	YES	☐	NO
Paraffin	☐	YES	☐	NO

Other _____

23. What is the main method of heating in your child's bedroom?

	1		2	
Coal fire	☐	YES	☐	NO
Electric units	☐	YES	☐	NO
Gas units	☐	YES	☐	NO
Central heating	☐	YES	☐	NO
Paraffin	☐	YES	☐	NO

Other _____

24. In which room do you have carpets or rugs ?

	1		2	
Living room	☐	YES	☐	NO
Bedroom	☐	YES	☐	NO

25. How frequently do you vacuum ? (Give number of days per week) ☐ Days

26. Is your house troubled with dampness ? 1 ☐ YES 2 ☐ NO

	1		2	
Rising dampness	☐	YES	☐	NO
Condensation	☐	YES	☐	NO
Penetrating dampness	☐	YES	☐	NO

27. During the past 12 months has your child visited your family doctor with an illness or been admitted to hospital ?

	1		2	
Family Doctor	☐	YES	☐	NO
Hospital	☐	YES	☐	NO

28. Name and address of your family doctor.

_____

_____

_____

_____

PART B WHEEZE

1. Has your child ever had an attack of wheezing (by wheezing I mean noisy breathing with a whistling sound coming from the chest not the throat)?.

1 YES ☐ IF YES CONTINUE 2 NO ☐ IF NO CONTINUE TO PART C

2. Has your child sometimes woken at night wheezing ?

1 ☐ NO
2 ☐ YES during the last 12 months
3 ☐ YES but prior to the last 12 months

3. Has your child sometimes been particularly wheezy first thing in the morning ?

1 ☐ NO
2 ☐ YES during the last 12 months
3 ☐ YES but not for the last 12 months

4. What length of time does morning or night wheeze usually last ?

1 ☐ Less than 15 minutes
2 ☐ HALF hour
3 ☐ HALF to ONE hour
4 ☐ Longer than ONE hour

5. At what age did you first notice your child wheezing ?

☐☐ Years ☐☐ Months

6. At what age did you last notice your child wheezing ?

☐☐ Years ☐☐ Months

7. Did your child wheeze before or after attending school ?

	1	2
Before	☐ YES	☐ NO
After	☐ YES	☐ NO

8. Has your child wheezed at any time during the last 12 months?

1 ☐ YES 2 ☐ NO

9. Does your child wheeze usually following an infection ?

1 ☐ YES 2 ☐ NO

10. In which season (s) do you notice your child's wheeze ?

	1	2
Spring	☐ YES	☐ NO
Summer	☐ YES	☐ NO
Autumn	☐ YES	☐ NO
Winter	☐ YES	☐ NO

11. Over the last 12 months what has been the longest period without any wheezing ?

1 ☐ Less than 1 week
2 ☐ 1 week to 1 month
3 ☐ 1 month to 3 months
4 ☐ Longer than 3 months

SHORTNESS OF BREATH

PART ℂ

Has your child ever been either unexpectedly breathless at rest or more breathless than you would expect after exercise (by breathless I mean out of breath or puffed) ?

1 YES ☐ IF YES CONTINUE

2 NO ☐ IF NO CONTINUE TO PART 𝔻

1. Has your child sometimes woken at night breathless ?

1 ☐ NO
2 ☐ YES, during the last 12 months
3 ☐ YES, but not for the last 12 months

2. Has she / he sometimes been particularly breathless first thing in the morning ?

1 ☐ NO
2 ☐ YES, during the last 12 months
3 ☐ YES, but not for the last 12 months

3. Ifyour child has shortness of breath how long does it usually last ?

1 ☐ Less than 15 minutes
2 ☐ HALF hour
3 ☐ HALF to ONE hour
4 ☐ Longer than ONE hour

4. Around what age did you first notice your child breathless ? ☐☐ Years ☐☐ Months

5. Around what age did you last notice your child breathless ? ☐☐ Years ☐☐ Months

6. Did your child have shortness of breath before or after attending school

	1	2
Before	☐ YES	☐ NO
After	☐ YES	☐ NO

7. Has your child been breathless at any time during the last 12 months ? ☐ YES ☐ NO

8. Does your child's shortness of breath usually follow an infection ☐ YES ☐ NO

9. In which season(s) do you notice your child has shortness of breath

	1	2
Spring	☐ YES	☐ NO
Summer	☐ YES	☐ NO
Autumn	☐ YES	☐ NO
Winter	☐ YES	☐ NO

10. Over the last 12 months what has been the longest period without breathlessness ?

☐ Less than 1 week
☐ 1 week to 1 month
☐ 1 month to 3 months
☐ Longer than 3 months

PART D · COUGH

1. Has your child ever seemed to cough more (or to get more coughs) compared to other children ?

1 ☐ NO
2 ☐ YES during the last 12 months
3 ☐ YES but not for the last 12 months

2. Has your child ever woken at night with coughing for 3 or more nights in a row (apart from during the first 5 days of a cold) ?

1 ☐ NO
2 ☐ YES during the last 12 months
3 ☐ YES but not for the last 12 months

3. Has your child sometimes had a tendency to cough first thing in the morning ?

1 ☐ NO
2 ☐ YES, during the last 12 months
3 ☐ YES, but not for the last 12 months

4. When your child has a cough for what length of time does it last?

1 ☐ Less than 15 minutes
2 ☐ Up to HALF hour
3 ☐ HALF to ONE hour
4 ☐ Longer than ONE hour

5. What has your doctor told you is the cause of this, if anything ?
(You can tick more than one box)

Chest infection	1 ☐ YES	2 ☐ NO
Bronchitis	☐ YES	☐ NO
Croup	☐ YES	☐ NO
Asthma	☐ YES	☐ NO
None of these	☐ YES	☐ NO

6. How many days has your child lost from school with cough or wheeze or breathlessness over the past 12 months ?

1 ☐ None
2 ☐ 1 to 5
3 ☐ 6 to 20
4 ☐ More than 20

7. Has your child ever been admitted to hospital for a day or more with wheezing or breathlessness ?

1 ☐ NO
2 ☐ YES, during the last 12 months
3 ☐ YES, but not for the last 12 months

PART E COUGHING/ WHEEZING/ BREATHLESSNESS

During the last 12 months have you particularly noticed that any of the following have tended to make your child cough or wheeze or become breathless.

	Breathlessness or wheezing		Cough	
	1	2	1	2
1. Particular places (eg. on holiday or in someone else's house.)	☐ YES	☐ NO	☐ YES	☐ NO
2. Changes of temperature (eg. going from a warm to a cold room.)	☐ YES	☐ NO	☐ YES	☐ NO
3. Head colds	☐ YES	☐ NO	☐ YES	☐ NO
4. Infection	☐ YES	☐ NO	☐ YES	☐ NO
5. Emotion (eg. stress, anxiety, laughing or crying)	☐ YES	☐ NO	☐ YES	☐ NO
6. Weather (eg. windy, cold, damp, humid.)	☐ YES	☐ NO	☐ YES	☐ NO
7. Exercise (eg. vigorous sports, running etc,)	☐ YES	☐ NO	☐ YES	☐ NO
8. Household chemicals (eg. bleach, hair spray, perfumes, etc,.)	☐ YES	☐ NO	☐ YES	☐ NO
9. Things around your child (eg. dusting, bed making, hoovering, pets, mowing grass, feather quilts, pillows or cushions)	☐ YES	☐ NO	☐ YES	☐ NO
10. Smoke and fumes:-	☐ YES	☐ NO	☐ YES	☐ NO
Cigarettes	☐ YES	☐ NO	☐ YES	☐ NO
Traffic fumes	☐ YES	☐ NO	☐ YES	☐ NO
Coal dust	☐ YES	☐ NO	☐ YES	☐ NO
Grain	☐ YES	☐ NO	☐ YES	☐ NO

Other substances - specify _____

During the last 12 months has your child ever appeared to suffer from chest pain or discomfort or chest tightness

1 ☐ YES 2 ☐ NO

Does your child sometimes have difficulty sleeping because of chestiness ?

1 ☐ YES 2 ☐ NO

Appendix B

Additional questions used in 1993

1. Did the child's mother smoke during pregnancy ?

Yes ☐ 1 No ☐ 2

2.. Did the child's father during the mother's pregnancy ?

Yes ☐ 1 No ☐ 2

Appendix C

Parent information document

South Sefton (Merseyside) Health Authority

District Headquarters, Fazakerley Hospital
Longmoor Lane, Liverpool L9 7AL
Telephone 051-525 3622
Fax. 051-525 6086

(Please quote our reference in reply)

Our Ref.

Your Ref.

When telephoning or calling please ask for

.....

Dear Parent,

re: Questionnaire on Asthma in children

In recent months, concern has been expressed about the frequency of asthma attacks and wheezing episodes in some of the school children within this district.

This questionnaire will help us to determine what basis there is for this concern.

The information given in this questionnaire will remain confidential at all times. We appreciate the help you are giving us by filling in and returning the questionnaire.

Thank you for your co-operation.

Yours sincerely,

Dr. M.J. Smith

CONSULTANT COMMUNITY PAEDIATRICIAN

Appendix D

Dust pollution measurements

Table 1. British Standard gauge results - total undissolved solids

	Exposed area		*Control area 2*
	Site 1	*Site 2*	
April 1991 - March 1992			
N° of monthly samples available	12	4*	2*
Mean (mg/m²/day)	153.1	113.3	25.4
Max. recorded value†	456.0	181.6	31.5
Min recorded value†	66.9	67.3	19.2
March 1993 - January 1994			
N° of monthly samples available	11	11	2*
Mean (mg/m²/day)	107.3	143.2	34.6
Max. recorded value†	288.1	297.2	39.6
Min recorded value†	38.7	56.4	29.5

* Low N° due to vandalism

† At any sample site

Table 2. Frisbee type gauge results* - total undissolved solids

	Exposed area (17 sites)	*Control area 2 (2 sites)*
March 1991 - March 1992		
N° of fortnightly samples available	382	36
Mean (mg/m²/day)	104.2	36.2
Max. recorded value†	401.2	79.1
Min recorded value†	22.9	8.6
March 1993 - March 1994		
N° of fortnightly samples available	421	51
Mean (mg/m²/day)	66.9	31.3
Max. recorded value†	406.4	121.3
Min recorded value†	8.7	5.9

* Frisbee type gauge provides dust deposition measurements

† At any sample site

Appendix E

Questionnaire for case-control study

CHILDREN'S QUESTIONNAIRE

ALL INFORMATION CONTAINED IN THIS DOCUMENT IS CONFIDENTIAL

Questionnaire N°. ☐☐☐☐

Child's Name _____

Home address _____

_____

_____

Postcode ☐☐☐☐☐☐

Tel N° _____

School _____ Class _____

Child's age Years ☐☐ Months ☐☐

Sex Boy ☐$_1$ Girl ☐$_2$

Family Doctor _____

Address _____

Tel N° _____

PART A - ABOUT THE MOTHER

1. What was the mothers age when the survey child was born ?

   Years ☐☐

2. Did the mother suffer any illnesses during the pregnancy

   ☐$_1$ ☐$_2$

   If "yes" please give details

   _____

   _____

3. Do you have any other children ? ☐$_1$ ☐$_2$

   If "yes" how many ? ☐☐

2 What position in the sibship does _____ occupy ? ☐

Please give details of your other children

	S	Age		Live status		Asthma		Hayfever		Eczema	
NAME		Y	M	Y_1	N_2	Y_1	N_2	Y_1	N_2	Y_1	N_2

4. Does the mother or the father of the child have asthma ?

Mother ☐1 ☐2

Father ☐1 ☐2

If "no" has the mother or father ever had asthma ?

Mother ☐1 ☐2

Father ☐1 ☐2

If either parent has asthma what medications are used ?

Mother Releiver ☐1 ☐2

Preventer ☐1 ☐2

Father Releiver ☐1 ☐2

Preventer ☐1 ☐2

5. Has the child's mother or father ever had hayfever or eczema ?

Mother Hayfever ☐1 ☐2

Eczema ☐1 ☐2

Father Hayfever ☐1 ☐2

Eczema ☐1 ☐2

PART B - ABOUT THE CHILD

1. Has your child ever been diagnosed by a doctor as having asthma ?

   ☐$_1$ ☐$_2$

   If "yes" was it by your GP ? ☐$_1$ ☐$_2$

2. Has your child been treated for asthma in the past year ? ☐$_1$ ☐$_2$

3. Is your child taking any medication(s) at present ? ☐$_1$ ☐$_2$

   if "yes" which of the following

Inhaled Bronchodilator	☐$_1$	☐$_2$
Inhaled steroid	☐$_1$	☐$_2$
Oral bronchodilator	☐$_1$	☐$_2$
Oral steroid	☐$_1$	☐$_2$
Intal/cromoglycate	☐$_1$	☐$_2$
Nedcromil	☐$_1$	☐$_2$
Nebuliser	☐$_1$	☐$_2$
Other	☐$_1$	☐$_2$

4. Is your child's asthma well controlled ? ☐$_1$ ☐$_2$

   If "no" can you suggest a way of improving your child's asthma management ?

   _____

5. What was the birthweight of your child

   Pounds ☐☐ ounces ☐☐

6. Was your child born prematurely ? ☐1 ☐2

If "yes" did a doctor, midwife or nurse tell you that your child was premature or is this based on your own estimation ?

Doctor/Midwife/Nurse ☐1 Self ☐2

If "self" what do you mean by premature ?

N° Days ☐☐

7. Was your child born at hospital or home ?

Hospital ☐1 Home ☐2

Which hospital ? _____

8 Was the child breast fed ?

No ☐1

< 1 month ☐2

1-3 months ☐3

> 3 months ☐4

9. Did the child have any respiratory illnesses when aged less than two ? years?

☐1 ☐2

10. Was your baby ever admitted to the Special Care Baby Unit due to breathing difficulties ?

☐1 ☐2

11. If "yes", how long was he/she on the unit ? ☐☐ days

Was the baby helped to breath with a machine ? ☐1 ☐2

12. Has your child been to the hospital in the past 12 months with chest problems ?

☐1 ☐2

If "yes" how many times ☐☐

13. Does your child have hayfever or eczema ?

Hayfever ☐1 ☐2

Eczema ☐1 ☐2

14. Does your child have any allergies ? ☐1 ☐2

15. Has your child had wheezing in the past 12 months ? (by wheezing I mean a whistling or wheezing noise coming from the throat or chest)

☐1 ☐2

16. Has your child been unexpectedly breathless in the past 12 months, at rest or more breathless than you would expect after exercise ?

☐1 ☐2

17. Has your child had excess cough in the past 12 months (that is coughed more or gotten more coughs compared to other children) ?

☐1 ☐2

18. Does your child cough after exercise ?

No ☐1 Not very often ☐2 Often ☐3

19. Does our child cough at night ?

No ☐1 Only with a cold ☐2 Often ☐3

20. Do colds go to your child's chest ? ☐1 ☐2

21. When your child coughs does he/she bring up phlegm ? ☐1 ☐2

22. Has your child been vaccinated against the following

Diptheria	☐1	☐2
Polio	☐1	☐2
Whooping cough	☐1	☐2
Tetanus	☐1	☐2
Measles	☐1	☐2

23. Does your child have any of the following ?

Diabetes	☐1	☐2
Seizures/Fits	☐1	☐2
Cystic Fibrosis	☐1	☐2
Eye problems	☐1	☐2
Hearing/Ear problems	☐1	☐2
Speech problems	☐1	☐2
Skin infections	☐1	☐2
Water infections	☐1	☐2
Learning difficulties	☐1	☐2
Surgery	☐1	☐2
Other	☐1	☐2

Please specify _____

24. Does your child's health affect his/her school performance ? ☐1 ☐2

25. How many days has your child lost from school in the past 12 months due to cough, wheeze or breathlessness ?
☐☐

26. How many days has your child lost from school in the past 12 months due to other reasons ?
☐☐

PART C - ABOUT THE HOME

1. Does your home have damp patches on the walls ?

   No ☐1 A few ☐2 A lot ☐3

2. Is there any mould in the following rooms ?

   Living room ☐1 ☐2

   Child's bedroom ☐1 ☐2

   Bathroom ☐1 ☐2

3. Does your home have central heating ? ☐1 ☐2

4. Does your home have an electric fire ? ☐1 ☐2

5. Does your home have a gas/coal fire ? ☐1 ☐2

6. For cooking do you use

   Gas ☐1

   Electricity ☐2

   Both ☐3

   Other ☐4

7. Does any person in the household smoke ? ☐1 ☐2

8. Has the mother ever smoked ? ☐1 ☐2

   If "yes" did she/you smoke during pregnancy ? ☐1 ☐2

   First half of pregnancy ☐1 ☐2

   Second half of pregnancy ☐1 ☐2

Appendix F

Dietary diary

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

CONFIDENTIAL

Name: .....

Address : .....

.....

.....

.....

Telephone : .....

Survey Days : 1. .....
2. .....
3. .....

If you have concerns or queries with any part of this survey please contact Mrs. Lynne Burgess

Tel: .....

OFFICIAL USE ONLY

HOW TO COMPLETE YOUR THREE DAY DIET DIARY

1. Use this booklet to record ALL FOOD and DRINK consumed on each of the three (3) days shown on the front page.
2. Write down the TIME, the AMOUNT, and DESCRIPTION of all food and drink consumed on that day, including MEALS and SNACKS eaten outside the home. Please also record any LEFTOVERS
3. If VITAMIN supplements are taken please give the BRAND NAME and the NUMBER taken each day.

PLEASE GIVE AS MUCH INFORMATION AS POSSIBLE FOR EXAMPLE :

(a). Type of food eaten, Eg. Semi skimmed milk

(b). Amount eaten eg. (2 slices), (3 slices), (3 tablespoons).

(c). Cooking method eg. potatoes boiled in salted water, chips cooked in vegetable oil.

(d). Wherever possible give the brand name eg. Heinz beans

(e). Where necessary state whether the food is fresh, tinned or frozen.

(f). Record any sauces or dressings eaten eg. tomato ketchup, gravy, mayonnaise

IMPORTANT

Please make sure you record everything consumed including **SWEETS, DRINKS AND SNACKS.**

An example of this part of a day's diary is shown below:

Time	Amount	Food or Drink
8.30	2	Weetabix
	Teaspoon	Sugar
	1/4 pint	Skimmed milk
10.15	Cup	Instant coffee with whole milk
	Fun size	Mars Bar
12.30		Holland's chesse pie
	Large	Banana - left half
	Can	Lemonade
5.15	Cup	Tea with skimmed milk
	Large thick	Whole meal bread
	slice	
	1/4 teaspoon	Marmite butter spread thinly
7.00	Cup	Boiled white rice
	1/2	Tesco's vegetable curry
	350 g tin	
		Ski strawberry yoghurt

Day one ....

Time	Amount	Food or Drink

me	Amount	Food or Drink

Day two .....

Time	Amount	Food or Drink

ime	Amount	Food or Drink

Day three ....

Time	Amount	Food or Drink

me	Amount	Food or Drink

Time	Amount	Food or Drink

...	Amount	Food or Drink

Appendix G

Publications

Thorax 1995;50:525-530

Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside

Y J Kelly, B J Brabin, P Milligan, D P Heaf, J Reid, M G Pearson

Abstract

Background **– A study was carried out to analyse the impact of maternal asthma on the risk of preterm delivery and the contribution of preterm delivery to the development of childhood asthma.**

Methods **– Two cross sectional community studies of 1872 children (5–11 years) in 1991 and 3746 children in 1993 were performed. A respiratory health questionnaire was distributed throughout 15 schools in Merseyside and completed by the parents of the children.**

Results **– Asthmatic mothers were more likely to have a preterm delivery than non-asthmatic mothers (odds ratio (OR) 1·49; 95% CI 1·10 to 2·02). Smoking was a separate risk factor for preterm delivery (OR 1·35; 95% CI 1·10 to 1·65). Asthmatic mothers did not have an increased risk of delivering small, growth retarded babies. Maternal asthma, paternal asthma, and premature birth, in that order, increased the risk of later childhood respiratory morbidity (OR 3·13, 95% CI 2·36 to 4·16; 2·23, 95% CI 1·62 to 3·05; 1·40, 95% CI 1·10 to 1·79). Conversely, babies who were small for gestational age appeared less likely to develop doctor diagnosed asthma or the symptom triad of cough, wheeze, and breathlessness in childhood, although this was not statistically significant (OR 0·63, 95% CI 0·28 to 1·41).**

Conclusions **– Maternal smoking during pregnancy and maternal asthma are independent risk factors associated with preterm delivery. Asthma in mothers predisposes to preterm delivery but not fetal growth retardation. Preterm birth, but not growth retardation, predisposes the child to the development of subsequent asthma.**

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In a study of children born in one week in 1970,[1] wheezing at the age of five was reported to be more common in those who were born prematurely or who were of low birthweight. There are a number of possible explanations for this; small, premature infants are more prone to respiratory illnesses in early life which can result in airways obstruction and impaired lung function.[2] There is an effect of maternal smoking on preterm delivery, low birthweight, and infant lung function.[3] Children of asthmatic mothers are at increased risk of atopic disease and bronchial hyperreactivity,[4,5] and it has been suggested that maternal asthma may predispose to premature labour.[6,7] Hyperactivity of uterine smooth muscle could occur in women with bronchial hyperresponsiveness and β agonists might be beneficial in prolonging gestation.[8] There is some evidence that asthmatic mothers not requiring inhaled β agonist bronchodilators during pregnancy have a higher incidence of low birthweight babies.[9] However, a recent controlled prospective study did not significantly associate use of inhaled bronchodilators with preterm births, low birthweight, or adverse perinatal outcome.[10]

These studies do not report on respiratory outcome in children for whom both perinatal outcome, parental history of asthma, and smoking during pregnancy are known. This paper is a further analysis of a study designed to collect information on environmental exposures and respiratory symptoms in primary schoolchildren for whom we had data on perinatal outcome (shown as prematurity and birthweight), as well as current respiratory symptoms, 5–11 years later. We have analysed the impact of maternal asthma on prematurity and birthweight and the subsequent effect of all of these factors on the development of respiratory symptoms in children.

Methods

STUDY DESIGN

A cross sectional survey to determine the prevalence of respiratory symptoms in primary schoolchildren (5–11 years) was performed between October and December 1991 in three communities in Merseyside. Briefly, in 1991 a parent-completed questionnaire was distributed to every alternate child on the class register in five schools in each of the three communities. All communities were recognised as having major housing and unemployment problems, and one of the areas was known to be exposed to increased levels of air pollution. The general data and detailed methods are reported elsewhere.[11] This survey indicated a probable association between maternal asthma and preterm delivery. In the same months of 1993 a second survey of a larger sample which included all children in the same school population was performed, using the same questionnaire, but with additional questions relating to pregnancy, history of smoking, and maternal

Table 1 Prevalence of preterm delivery in 1991 and 1993 in relation to parental asthma

Survey group and year	Prevalence of preterm delivery (%)	
	Parent asthmatic	Parent non asthmatic
1991		
Mother	23·7 (28/118)	14·0 (220/1574)
Father	16·7 (17/102)	14·1 (220/1559)
1993		
Mother	19·1 (61/319)	13·0 (410/3158)
Father	14·7 (31/232)	13·2 (405/3066)

medication for asthma. The larger sample size in the second survey enabled the associations and statistical significance between maternal asthma and preterm delivery to be assessed in detail.

QUESTIONNAIRE

The questionnaire was adapted and modified from a questionnaire designed by Clifford *et al*.[12] It included questions on factors related to risk of preterm delivery including maternal and paternal socioeconomic factors, employment status, and smoking of either parent during the pregnancy or subsequently. The birthweight of the child was requested and preterm delivery was defined according to the parental response to the question "Was your baby born prematurely?" Several factors related to the risk of asthma in the children were requested, and included type of dwelling (carpets, dampness); type of heating; presence of furry pets in the home; type of infant feeding; family history of allergy; and exposure to air pollutants. Wheeze and dyspnoea were identified by the questions "Has your child ever had an attack of wheezing (by wheezing I mean noisy breathing and a whistling sound coming from the chest or throat)?" and "Has your child ever been either unexpectedly breathless at rest or more breathless than you would expect after exercise (by breathless I mean out of breath or puffed)?" The question used to identify abnormal cough was "Has your child ever seemed to cough (or get more coughs) than other children?" All parents were asked if their child had ever been diagnosed by a doctor as having asthma or bronchial asthma. Parental asthma was identified with the question "Does the child's mother or father suffer from asthma?" and maternal smoking during pregnancy with the question "Did the mother or father of this child smoke during the mother's pregnancy?"

Questionnaires were delivered to schools and surveys completed concurrently in South Sefton, Waterloo, Netherton, and Bootle (north and east of the Mersey estuary), and Wallasey (south of the Mersey estuary). Children returned questionnaires during the following two week period. Repeat visits to schools were made by a research worker for absentees. Ethical approval for the study was given by the South Sefton ethical committee. Children were defined as low birthweight if <2·5 kg at delivery and preterm according to the parental response to the prematurity question. Small for gestational age infants were those reported as full term babies whose birthweight was <2·5 kg.

STRATIFIED ANALYSIS

Contingency tables were analysed using hierarchical log linear modelling. Odds ratios calculated for the main effects of interest were adjusted for confounders using logistic regression. Potential confounders were of three main types: socioeconomic, environmental, and factors related to predisposition.

Results

In 1991 a total of 1872 questionnaires were returned out of 2035 sent to parents (92%). In the second survey in 1993 a total of 3746 out of 4288 sent to parents were returned (87%); 1093 children were surveyed on both occasions. Of the 1991 respondents 97·1% answered the question on preterm delivery and 95·9% provided their child's birthweight. In 1993 the figures were 97·4% and 96·8%, respectively. Response rates for the main respiratory variables in 1991 were 89·5% (doctor diagnosed asthma), 85·8% (wheezing), 86·6% (breathlessness), and 90·1% (cough). Very similar response rates were observed for the 1993 survey. For parents who completed the questionnaire in both surveys the agreement between answers on prematurity and birthweight were 97% and 98%, respectively. The mean difference in birthweights that did not match was small (168 g). The agreement for respiratory symptoms was doctor diagnosed asthma (93·1%), wheezing (69·9%), breathlessness (62·1%), maternal asthma (89·7%), and paternal asthma (77·8%).

MATERNAL ASTHMA AND PRETERM BIRTH

In both surveys there was a significant increase in reported preterm delivery associated with maternal but not paternal asthma (table 1).

Table 2 Prevalence of preterm, growth retarded, and full term deliveries in relation to parental asthmatic status (1993 survey)

Parent	Asthmatic parent					Non-asthmatic parent			
	Full term		Preterm			Full term		Preterm	
	<2·5 kg*	≥2·5 kg†	<2·5 kg	≥2·5 kg		<2·5 kg*	≥2·5 kg†	<2·5 kg	≥2·5 kg
Mother [n = 317]	3 (0·9)	253 (79·8)	24 (7·6)	37 (11·7)	[n = 3120]	58 (1·9)	2657 (85·1)	162 (5·3)	243 (7·8)
Father [n = 229]	2 (0·9)	193 (84·3)	13 (5·7)	21 (9·2)	[n = 3030]	54 (1·8)	2573 (84·9)	155 (5·1)	247 (8·2)

* Small for gestational age (full term and <2·5 kg birthweight).
† Appropriate for gestational age (full term and ≥2·5 kg birthweight).
Numbers in parentheses are percentages. Associations among preterm delivery, low birthweight (<2·5 kg), paternal and maternal asthma were assessed by log linear analysis of the four-way table. The best fitting hierarchical model showed two significant associations: preterm birth and low birthweight ($p<0·001$); maternal asthma and preterm birth ($p = 0·02$).

Table 3 Odds ratio for preterm delivery among mothers in relation to asthmatic status and cigarette smoke exposure during pregnancy

Maternal asthmatic and pregnancy smoking status	Prevalence (%) of preterm delivery	Unadjusted odds ratio* (95% CI)
Asthmatic and smoker	19·8	1·91 (1·18 to 3·06)
Asthmatic and non-smoker	17·5	1·63 (1·07 to 2·49)
Non-asthmatic and smoker	15·3	1·39 (1·11 to 1·73)
Non-asthmatic and non-smoker	11·5	

*Compared with non-asthmatic, non-smoking mothers.

Table 4 Adjusted odds ratios for preterm delivery from multiple logistic regression

Variable	Odds ratio	95% confidence interval
1991 survey (n = 1715)		
Maternal asthma	1·89	1·21 to 2·96
Any smokers in household	1·64	1·22 to 2·19
1993 survey (n = 1403)		
Maternal asthma	1·49	1·10 to 2·02
Mother smoking during pregnancy	1·35	1·10 to 1·65

Table 5 Prevalence of respiratory morbidity in children in relation to prematurity by parental asthmatic status (1993 survey)

Parental asthmatic status and childhood respiratory outcome	Birth category	
	Full term	Preterm
Asthmatic mother		
Ever diagnosed asthma	41·4 (106/256)	45·8 (27/59)
Cough, wheeze, breathlessness	17·8 (35/197)	16·3 (7/43)
Asymptomatic	49·2 (97/197)	53·5 (23/43)
Non-asthmatic mother		
Ever diagnosed asthma	19·0 (513/2694)	26·7 (102/382)
Cough, wheeze, breathlessness	5·6 (129/2299)	10·5 (35/334)
Asymptomatic	72·6 (1668/2299)	63·2 (211/334)
Asthmatic father		
Ever diagnosed asthma	36·1 (70/194)	55·9 (19/34)
Cough, wheeze, breathlessness	13·3 (21/158)	25·0 (5/24)
Asymptomatic	52·5 (83/158)	37·5 (9/24)
Non-asthmatic father		
Ever diagnosed asthma	19·6 (512/2607)	24·9 (99/397)
Cough, wheeze, breathlessness	5·9 (130/2209)	10·3 (34/331)
Asymptomatic	70·1 (1548/2209)	66·2 (219/331)

Ever diagnosed asthma = asthma diagnosed by a doctor; cough = excess cough in previous 12 months; wheeze = attack of wheezing at any time; breathlessness = attack of breathlessness at any time.

Table 6 Prevalence of respiratory morbidity in children in relation to fetal growth retardation by parental asthma status (1993 survey)

Parental asthmatic status and childhood respiratory outcome	Birth category	
	Full term (≥2·5 kg)	Full term (<2·5 kg)*
Asthmatic mother		
Ever diagnosed asthma	40·1 (103/253)	0·0 (0/3)
Cough, wheeze, breathlessness	17·9 (35/196)	0·0 (0/1)
Asymptomatic	49·5 (97/196)	0·0 (0/1)
Non-asthmatic mother		
Ever diagnosed asthma	19·2 (506/2636)	13·8 (8/58)
Cough, wheeze, breathlessness	5·7 (128/2251)	2·1 (1/48)
Asymptomatic	72·5 (1633/2251)	72·9 (35/48)
Asthmatic father		
Ever diagnosed asthma	36·5 (70/192)	0·0 (0/2)
Cough, wheeze, breathlessness	13·4 (21/157)	0·0 (0/1)
Asymptomatic	52·2 (82/157)	100·0 (1/1)
Non-asthmatic father		
Ever diagnosed asthma	19·8 (505/2553)	13·0 (7/54)
Cough, wheeze, breathlessness	6·0 (129/2164)	2·2 (1/45)
Asymptomatic	72·4 (1566/2164)	71·1 (32/45)

*Small for gestational age.
Ever diagnosed asthma = asthma diagnosed by a doctor; cough = excess cough in previous 12 months; wheeze = attack of wheezing at any time; breathlessness = attack of breathlessness at any time.

The prevalence of preterm delivery among the 2652 children surveyed in 1993 but not in 1991 was 17·1% for asthmatic and 13·0% for non-asthmatic mothers. Children in the 1993 survey were separated into birth categories determined by birthweight (<2·5 kg or ≥2·5 kg) and prematurity status. Significantly more preterm babies were born to asthmatic mothers (table 2), but amongst these preterm babies asthma did not significantly increase the risk of low birthweight (<2·5 kg). The mean (SD) birthweight of preterm babies over 2·5 kg was 2·62 (0·64) kg which corresponds to a 50th percentile at 34·5 weeks gestation on the Tanner and Thomson growth charts.[13] No difference in prevalence of growth retarded babies (full term gestation and <2·5 kg) was observed in relation to parental asthmatic status. The mean (SD) birthweights for growth retarded full term and normal full term infants were 2·25 (0·19) kg and 3·47 (0·46) kg, respectively.

Maternal asthma and smoking during pregnancy each increased the risk of preterm delivery. Table 3 shows the unadjusted odds ratios for the various categories of mothers. Asthmatic mothers who smoked were at the highest risk. Logistic regression was used to calculate adjusted odds ratios for the effects of smoking and asthma. This was done separately for the 1991 and 1993 surveys (table 4). In both 1991 and 1993 maternal asthma was the predominant risk factor for preterm delivery. "Any smokers in the household" was the only significant risk factor identified for the 1991 model. The 1993 survey showed that it was maternal smoking during pregnancy, rather than paternal smoking or other smokers in the household (that is, passive smoking), which was directly associated with increased risk of preterm delivery. There was no statistical interaction between maternal asthma and smoking, indicating that they had separate effects. Other health problems, allergies, and paternal unemployment – though significant when considered in isolation – did not have odds ratios significantly different from unity after adjustment for known confounders. Adding any more predictors did not significantly improve the models nor change the parameter estimates. Information on maternal parity was not available on the questionnaire and could not be added to the model. Maternal smoking during pregnancy was not associated with increased risk of delivering a baby that was small for gestational age (odds ratio (OR) 1·63, 95% CI 0·97 to 2·73).

PARENTAL ASTHMA, BIRTHWEIGHT, PREMATURITY, AND LATER CHILDHOOD RESPIRATORY MORBIDITY

Adjusted odds ratios were estimated using logistic regression analysis of the data in table 5 and showed an effect of maternal asthma (OR 3·13; 95% CI 2·36 to 4·16); paternal asthma (OR 2·23; 95% CI 1·62 to 3·05), and preterm birth (OR 1·40; 95% CI 1·10 to 1·79) on increasing the risk of developing ever diagnosed asthma. Using the definition of asthma as the presence of cough, wheezing, and breathlessness, the analysis showed a similar pattern: maternal asthma (OR 3·30; 95% CI 2·17 to 5·03), paternal asthma (OR 1·94; 95% CI 1·16 to 3·25), premature birth (OR 1·89; 95% CI 1·29 to 2·76). A number of environmental,

socioeconomic, and predisposing factors contribute to the risk of respiratory morbidity in children. These include other allergies and health problems, young age, sex (boy), parental unemployment, household dampness, rented accommodation, and geographical area. Adjusting for each of these variables the odds ratio for developing ever diagnosed asthma in preterm babies was 1·41 (95% CI 1·06 to 1·87), and for developing cough, wheeze, and breathlessness 1·82 (95% CI 1·15 to 2·88). Smoking during pregnancy or passive smoking was not associated with any of the respiratory outcome variables in univariate tests in the 1993 data. It was therefore not an important confounder of the relationship between preterm birth and later respiratory symptoms.

Table 6 shows that infants in our survey born small for gestational age to either asthmatic or non-asthmatic parents were at reduced risk of developing asthmatic respiratory symptoms compared with full term normal birthweight babies. This difference did not reach statistical significance, the odds ratio for developing ever diagnosed asthma being 0·63 (95% CI 0·28 to 1·41) and for developing cough, wheeze, and breathlessness 0·37 (95% CI 0·05 to 2·73). These findings are of interest as the reduction in risk was consistent in the different groups and contrasted with the results for preterm infants.

Discussion

QUESTIONNAIRE

Studies which rely on self-administered questionnaires are limited by the reliability and validity of the instruments used. Similar questionnaires have been shown to yield reproducible answers,[14] although the National Child Development Study found that lifelong reports of asthma and reports over the previous year did not show good agreement.[15] The validity of the survey is dependent on the response rate, and our high compliance figures of 92% and 87% compare favourably with other surveys,[7] and reduce the effects of bias. Over 95% of our respondents answered the key questions relating to preterm delivery and birthweight.

For all the main respiratory symptom variables response rates were over 85%. The measure of agreement for important measures in those who completed both surveys was generally good, although it was only 62·1% for breathlessness. Ascertainment of prematurity by the question "Was your baby born prematurely?" is dependent on the mother's knowledge and understanding of gestational age at delivery, which may have been explained in a number of ways by the attending doctor or nurse. The validity of the answers is supported by the observation that the mean birthweight of babies above 2·5 kg and reported as preterm by the mother was 2·62 kg. This corresponds to the 50th percentile at 34·5 weeks gestation on the Tanner and Thomson growth charts.[11] Only four preterm infants were above the 97th centile for birthweight at 37 weeks gestation. This distribution of birthweights for the preterm group is comparable to reference percentiles for premature babies and supports the validity of parental recognition of preterm delivery. The prevalence of reported preterm delivery was 14% in the 1991 survey and 13% in the 1993 survey. Both these figures are appreciably higher than previous surveys using prospective data. A stronger case for the causality of the associations would be demonstrated if the validity of the preterm delivery data was confirmed against original birth registers. Current work in this study population is examining this information.

MATERNAL ASTHMA, SMOKING, AND PRETERM DELIVERY

Biological and obstetric factors can play an important part in determining gestational duration. A recent meta-analysis identified 43 factors associated with preterm delivery,[16] but did not mention maternal asthma as a significant risk factor. Our analysis indicates a significant association between maternal asthma and preterm birth but, amongst preterm births, asthma does not increase the risk of low birthweight. This suggests that the effect of maternal asthma is primarily to shorten gestation to 34–37 weeks rather than leading to very preterm delivery. The regression analysis which controlled for socioeconomic factors identified maternal asthma in both the 1991 and 1993 surveys as a risk factor for preterm delivery. Hypotheses to explain the association of maternal asthma and preterm delivery remain to be elucidated. An attractive theory is that of uterine smooth muscle hyperreactivity in women with bronchial hyperresponsiveness. The effect of β agonists in inhibiting labour supports this hypothesis, and asthmatic patients not using β agonist bronchodilators during pregnancy have been reported to have a higher incidence of low birthweight babies.[9] Our data cannot address issues such as whether it is the severity of asthma or its treatment or control that is important.

The 1991 survey showed smokers in the household as a significant factor in increasing risk of preterm delivery. The greater detail on parental smoking collected in 1993 showed that maternal smoking during pregnancy was the important risk factor and not the passive effects of paternal smoking. Maternal asthma and maternal smoking appear to have independent and separate effects on increasing the incidence for prematurity. There is a large amount of literature on maternal smoking as an adverse factor on intrauterine growth (with birthweight reductions of up to 200 g) and gestational duration.[17] Previous studies have suggested that the effect of passive smoking on mean birthweight was 2–10 times less than that of active smoking.[18] Maternal smoking could cause preterm delivery through several mechanisms. Nicotine may result in an increase in maternal catecholamines and consequent uterine vasoconstriction.[19]

Maternal smoking was not associated with an increased risk of delivering a small for dates baby although the confidence interval for the

odds ratio was close to significance (0·97 to 2·73). Many women do give up smoking in early pregnancy and do not consider themselves to have smoked during pregnancy when subsequently questioned. The question asked could not separate out this group and this question should be addressed to exclude possible confounding.

PREMATURE BIRTH AND CHILDHOOD ASTHMA

While it is well established that children who survive bronchopulmonary dysplasia have poor airway function at school age, the long term outcome for preterm infants who do not develop bronchopulmonary dysplasia has been little studied. This is particularly the case for preterm infants who are born with birthweights greater than 2·5 kg. Our analysis indicates that preterm, but not low birthweight, babies are at particular risk for developing childhood asthma. Of preterm babies born to asthmatic parents almost half have been diagnosed as asthmatic at some time by a doctor. Asthma diagnosed by a doctor at some time could significantly overstate the current problem so we also defined a group of children with the symptom triad of cough, wheeze, and breathlessness on the grounds that the occurrence of all three together was most likely to be asthma. This symptom triad is also highly significantly associated with having been born prematurely, although the absolute risk is about half the genetic risk from having asthmatic parents.

We observed that the risk of asthma (doctor diagnosed or cough, wheeze, and breathlessness) was greater for premature babies. Babies born at full term but who were less than 2·5 kg - that is, small for gestational age - were less likely than either full term normal weight or preterm babies to develop the symptom triad of cough, wheeze, and breathlessness or doctor diagnosed asthma. This did not reach statistical significance and the percentage of asymptomatic children is similar to that in children born appropriate for gestational age. Nevertheless, this observation may be worth studying in a larger cohort. Could it be that growth retardation in utero in some way protects against asthma?

The relationship of prenatal and early postnatal events to lung function and airways responsiveness in schoolchildren has been studied prospectively for infants with birthweights less than 2000 g.[20 21] In these studies a reduction in airway function was observed in low birthweight children which was associated with cough but not wheeze. More recent research indicates that birthweight is related to lung size and methacholine responsiveness, and that prematurity and smoking during pregnancy appear to diminish airway size and increase the likelihood of exercise-induced bronchospasm or of asthma diagnosis.[22-24] A re-analysis controlling for confounding factors of the British National Birth Cohort of children born in one week of 1970 also confirms the original observations of Golding and Butler implicating low birthweight in the aetiology of childhood wheezing.[25 26]

Studies relating passive smoking, low birthweight, and prematurity have been reviewed recently[19] but the interrelationships of maternal asthma, active versus passive smoking by the parents, prematurity, and birthweight have not been systematically studied. Thus, if maternal asthma leads to prematurity and also influences the development of asthma, it is likely that univariate analysis will show prematurity associated with childhood asthma. Our data show that prematurity remains important even when the parental asthma is controlled, and also that it is the prematurity that is relevant regardless of birthweight.

A recent review of the literature[19] cites 13 references that implicate smoking in pregnancy as a factor in causing wheezing illness in children. Our data suggest that paternal smoking (passive to the unborn child) is not significant after adjusting for maternal smoking. This is probably because maternal and paternal smoking incidence is highly correlated. Thus, passive smoking may be relatively unimportant and future studies should concentrate on maternal smoking. Active smoking results in nicotine and other vasoactive substances reaching the circulation which could affect the fetus.

Chan *et al* have suggested a model of the aetiology of chronic respiratory morbidity in childhood based on birthweight, maternal smoking, genetic, and environmental factors.[20 21] They were unable to determine the relative importance of these factors because of the small size of their study. Analysis of our more extensive data suggests that several different pathways are involved in the development of recurrent cough and wheeze in childhood. Maternal asthma is associated with premature birth which is compounded if the mother smokes during pregnancy. Premature birth is associated with an increased risk of childhood wheezing and breathlessness, whether or not the parents are asthmatic. Maternal asthma is also associated with recurrent respiratory symptoms in children independently of whether the child is born preterm. Thus, it seems that there are several pathways by which asthma evolves.

Our results indicate the importance of preterm delivery in predisposing to recurrent cough and wheeze in children. If this is confirmed then it should be possible to target particular groups of mothers or preterm babies for intervention studies testing hypotheses related to causation. For example, premature babies of asthmatic mothers are at very high risk of childhood symptoms and would permit smaller longitudinal studies of asthma causation than would otherwise be possible. These are the obvious target groups upon which to test the effectiveness of interventions in the future.

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Clinical significance of cough and wheeze in the diagnosis of asthma

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Abstract

***Objectives*—(1) To determine the prevalence of cough, wheeze, and breathlessness, both as single symptoms and in combination, in primary schoolchildren and their relation to doctor diagnosed asthma. (2) To identify in areas with different levels of dust pollution whether questionnaire reported 'cough alone' (without wheeze or breathlessness) had similar risk factors to the questionnaire reported triad of 'cough, wheeze, and breathlessness'.**

***Subjects and methods*—Two cross sectional community surveys of primary schoolchildren (5–11 years) were performed in 1991 and 1993. Parent completed questionnaires related to socioeconomic and respiratory factors were distributed through 15 schools in three areas of Merseyside, one of which had a relatively high level of dust pollution. Data were analysed to determine the prevalence of different respiratory symptom patterns. Univariate and multiple logistic regressions were used to investigate the associations between respiratory symptom profiles and potential risk factors.**

***Results*—The proportions of completed questionnaires that were returned were similarly high in both surveys, 92% in 1991 (1872 of 2035) and 87% in 1993 (3746 of 4288). The proportions of children with different respiratory symptom patterns were similar in the two surveys: in 1991, asymptomatic children 70.1% (1109 of 1583), those with cough alone 8.9% (141 of 1583), and children with the symptom triad of cough, wheeze, and breathlessness 8.3% (132 of 1583); the figures for 1993 were 69.5% (2144 of 3083), 9.2% (284 of 3083), and 7.3% (224 of 3083) respectively. The prevalence of doctor diagnosed asthma increased from 17.4% in 1991 to 22.1% in 1993. The symptom of cough alone was associated with going to school in an area of increased air pollution. The symptom triad of cough, wheeze, and breathlessness was associated with reported allergies, familial history of atopy and preterm birth. In 1991, of children with the symptom of cough alone one in eight were diagnosed asthmatic; twice as many doctors made the diagnosis on this basis in 1993.**

***Conclusion*—The respiratory symptom of cough alone and cough, wheeze, and breathlessness represent clinical responses to different specific risk factors. Cough alone was associated with the environmental factors of school in the dust exposed zone and dampness in the home, whereas cough, wheeze, and breathlessness related to allergic history and preterm birth, and may be the best surrogate of asthma. Diagnosis of asthma on the basis of cough alone partly explains the increased prevalence of doctor diagnosed asthma, especially in dust polluted areas.**

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Many studies have reported the prevalence of asthma and of respiratory symptoms in children.[1–5] However, it is difficult to compare the results of different prevalence surveys because study populations have different socioeconomic profiles, environmental risk factors vary with time and between different areas, and the criteria used to define asthma differ. The pattern of respiratory symptoms can vary depending on the magnitude of specific risk factors in the area surveyed. It is necessary to distinguish which symptoms are associated with which risk factors in order to determine which group(s) of symptoms is/are the best surrogate of asthma and therefore estimate the true prevalence of asthma in groups of children with different respiratory symptom patterns.

We have re-examined questionnaire reported data from two cross sectional surveys performed in 1991 and 1993 to assess the possible impact of a dust pollution source on the respiratory health of primary schoolchildren on Merseyside. We previously reported in this population a 60% greater prevalence of excess cough (without wheeze and without breathlessness) in primary schoolchildren living in an area of increased dust pollution compared with other areas.[6] We were uncertain whether this increased reporting of cough alone represented an increase in asthma or whether it was a non-asthmatic response to increased levels of inhaled dust. We hypothesised that the symptom triad of cough with wheeze and breathlessness was likely to represent current symptomatic asthma and also examined questionnaire reported 'ever diagnosed asthma' which is

Table 1 General description of children for both surveys

	1991 (n=1872)	*1993 (n=3746)*
Mean age (years) (SD)	7.09 (2.0)	7.15 (2.0)
Sex (boy) (%)	51.0	50.2
Doctor diagnosed asthma (%)	17.4	22.1***
% Living in the area of increased air pollution	25.9	25.0
% With wheezing	20.6	21.3
% With breathlessness	12.8	12.7
% With cough	22.8	23.3

Wheezing: severe attack of wheezing at any time. Breathlessness: severe attack of breathlessness at any time. Cough: excess cough in the previous 12 months.
*** $p < 0.001$, compared with 1991. For other variables there was no significant difference between 1991 and 1993.

Table 2 Comparison of the prevalence (%) of respiratory symptom profiles in 1991 and 1993

	*1991 (n=1583)**	*1993 (n=3083)**
C−W−B−	70.1	69.5
C+W−B−	8.9	9.2
C+W+B+	8.3	7.3
C+W+B−	4.7	4.7
C−W+B−	4.1	5.0
C−W+B+	1.5	1.8
C+W−B+	1.7	1.1
C−W−B+	0.7	1.3

* Number of questionnaires returned with responses for all respiratory variables. C = excess cough in the previous 12 months; B = severe attack of breathlessness at any time; W = severe attack of wheezing at any time; + or − indicates the presence or absence of a symptom. The symptom patterns of cough alone (C+W−B−) and cough, wheeze, and breathlessness (C+W+B+) are more common than one would expect if the symptoms were independent of each other. Log linear analysis shows that there is a strong positive association between wheeze and breathlessness ($\chi^2 = 443$, $p < 0.001$). There is also a positive association between cough and wheeze ($\chi^2 = 197$, $p < 0.001$) and between cough and breathlessness ($\chi^2 = 104$, $p < 0.001$).

often used as a marker of asthma in prevalence studies.

In this paper our objectives were: (1) to determine the prevalence of cough, wheeze, and breathlessness either singly or in combination, (2) to identify whether questionnaire reported cough alone has similar risk factors to the questionnaire reported triad of cough, wheeze, and breathlessness, and (3) to compare the prevalence of doctor diagnosed asthma in children with different symptom patterns.

Subjects and methods

DESIGN

Two cross sectional community based surveys of primary schoolchildren (aged 5–11 years) were performed in 1991 and 1993 in five schools in each of three separate areas in Merseyside. In 1991 every second child on the class register was chosen for the survey (2035), and in 1993 all children in each school were surveyed (4288).

Table 3 Proportions of different symptom combinations for children with doctor diagnosed asthma

	1991 (n=237)	*1993 (n=533)*	*Significance level (p value)*
Cough, wheeze, and breathlessness (C+W+B+)	45.6	37.7	0.05
Cough or breathlessness with wheeze (C+B−W+ or C−B+W+)	30.7	32.5	0.71
Cough and/or breathlessness without wheeze (C+B+W− or C+B−W− or C−B+W−)	23.7	29.8	0.09

C = excess cough in the previous 12 months; B = severe attack of breathlessness at any time; W = severe attack of wheezing at any time; + or − indicates the presence or absence of a symptom.

QUESTIONNAIRE

The questionnaire was a modified version of that designed by Clifford *et al*[1] and has been fully described elsewhere.[6] Class teachers distributed and collected parent completed questionnaires which asked questions about parental smoking patterns, and socioeconomic and respiratory variables. Cough, wheeze, and breathlessness were assessed by the questions, 'has your child ever seemed to cough more (or get more coughs) compared to other children?'; 'has your child ever had wheezing (by wheezing I mean noisy breathing with a whistling sound coming from the chest or throat)?'; 'has your child ever been unexpectedly breathless at rest or more breathless than you would expect after exercise (by breathless I mean out of breath or puffed)?' The symptom triad of cough, wheeze, and breathlessness was deduced from positive responses to all three questions.

STATISTICAL METHODS

Two types of analysis were performed. Univariate analysis stratified for single risk factors and multiple logistic regression analysis were used to quantify risk factors associated with respiratory symptom profiles.

Results

The proportions of questionnaires returned were similarly high in both surveys, 1872 of 2035 (92%) in 1991 and 3746 of 4288 (87%) in 1993. Table 1 gives a general description of the study population. More children were diagnosed asthmatic by a doctor in 1993 but there were no differences in the overall prevalence of symptoms between the surveys (table 1).

The proportion of children with no symptoms, with the single symptom of cough, or with cough, wheeze, and breathlessness in combination were also similar in the two surveys (table 2).

In 1993 children with doctor diagnosed asthma were less likely to have the symptom triad of cough, wheeze, and breathlessness (37.7% *v* 45.6%), and more likely to have been labelled as asthmatic without ever having wheezed (29.8% *v* 23.7%) (table 3).

UNIVARIATE STRATIFIED ANALYSIS

A comparison of socioeconomic and maternal factors in 1991 and 1993 for asymptomatic children and those with cough alone and cough, wheeze, and breathlessness is shown in table 4. Univariate analysis showed that respiratory symptoms were significantly associated with renting rather than owning a property ($p<0.05$) and with the reported presence of dampness in the home ($p<0.01$), but not with the presence of smokers in the home or with having been breast fed. The symptom triad of cough, wheeze, and breathlessness was significantly associated with having been born prematurely ($p<0.01$).

Table 4 Frequency of socioeconomic and maternal variables (%) for children with different respiratory symptom profiles

	Respiratory symptom profile		
	Asymptomatic (n=1109)	Cough (n=141)	Cough, wheeze, breathlessness (n=132)
1991			
Rented accommodation	41.1	49.3	59.7***
Damp home	12.0	22.5**	31.4***
Smoker(s) in household	58.4	66.4	65.0
Preterm birth	12.5	13.7	26.0***
Not breast fed	68.2	66.2	67.9
1993	(n=2144)	(n=284)	(n=224)
Rented accommodation	42.9	54.7***	51.6*
Damp home	14.0	27.7***	30.5***
Smoker(s) in household	58.0	60.6	61.2
Mother smoked during pregnancy	36.0	34.3	35.1
Preterm birth	11.8	11.7	19.4**
Not breast fed	68.1	73.5	65.2

* p < 0.05, ** p < 0.01, *** p < 0.001, compared with asymptomatic children.

Table 5 Health parameters (%) in 1991 and 1993 for children with different respiratory profiles

	Respiratory symptom profile		
	Asymptomatic (n=1109)	Cough (n=141)	Cough, wheeze, breathlessness (n=132)
1991			
Doctor diagnosed asthma	2.1	10.0	83.1
Allergies (hay fever, eczema)	8.7	13.3	47.3
Prescribed medicines†	4.4	14.9	61.8
Absent from school due to respiratory symptoms for > 6 days/year	0.9	5.7	39.0
Ever admitted to hospital for respiratory symptoms	3.0	25.0	61.0
1993	(n=2144)	(n=284)	(n=224)
Doctor diagnosed asthma	3.0	22.6*	89.9
Allergies (hay fever, eczema)	12.9*	18.8	61.0*
Prescribed medicines†	5.2	22.9	75.1*
Absent from school due to respiratory symptoms for > 6 days/year	1.5	4.6	36.8
Ever admitted to hospital for respiratory symptoms	4.1	25.6	61.4

* p < 0.05, compared with 1991
† 65% of which are antiasthmatic medicines

In both surveys asymptomatic children were less likely to have doctor diagnosed asthma, allergies, medicines prescribed, admissions to hospital for respiratory symptoms, absenteeism from school (for more than six days) due to respiratory symptoms (all p<0.01), compared with children with cough alone or cough, wheeze, and breathlessness (table 5). Children with cough alone had a lower prevalence of each of these ill health indicators when compared with children with cough, wheeze, and breathlessness.

In 1993 the children with cough alone were more likely to have been diagnosed as asthmatic by a doctor (p<0.05) and to report problems with allergies. Significantly more children with the symptom triad received prescribed medicines in 1993 (p<0.05), although 25% were reported to be receiving no medication. In 1991, 2.1% (23 of 1109) and in 1993, 3.0% (63 of 2144) of asymptomatic children had a history of doctor diagnosed asthma. Although none of these children had current symptoms, 52% in 1991 (12 of 23) and 38% in 1993 (24 of 63) had a cough at some time in life which had been diagnosed as asthma. Reported diagnosis of asthma in other asymptomatic children remains unexplained.

REGRESSION ANALYSIS

Adjusted odds ratios for risk factors were calculated for respiratory symptom profiles by logistic regression in order to control for multiple confounding factors (table 6). Maternal asthma, allergies, and other health problems were strongly associated with cough, wheeze, and breathlessness. Preterm birth and paternal asthma were associated with cough and wheeze. The risk of cough and wheeze decreased with age (more steeply for cough). Of the other risk factors, some were associated with wheeze and some only with cough. Children with environmental risk factors such as going to school in the area of increased dust pollution, dampness in the home and rented accommodation were more likely to have cough alone.

Discussion

PREVALENCE OF RESPIRATORY SYMPTOM PROFILES

Questionnaires are often used in respiratory health surveys, and data collected in this way have been shown to be reproducible.[7 8] Confidence that the information collected is valid is dependent upon response rates, which in this study compared favourably with other reports.[1 5 9]

The two surveys were performed in parallel in the same areas and in the same months (October to December), avoiding variations due to seasonal influences. The prevalence of wheezing, cough, and breathlessness is comparable with previous reports.[4 5 10] The cumulative prevalence of doctor diagnosed asthma is higher than reported elsewhere, although this may be confounded partly by the low social class of the three areas in this study.

Table 6 Logistic regression models for cough, wheeze, and breathlessness for 1993 data; results are odds ratio (95% confidence interval)

	Cough	Wheeze	Breathlessness
Child has allergies	3.29 (2.50 to 4.33)	4.47 (3.36 to 5.94)	5.26 (3.79 to 7.29)
Maternal asthma	1.67 (1.65 to 2.43)	2.71 (1.87 to 3.93)	2.87 (1.91 to 4.33)
Child has other health problems	1.91 (1.44 to 2.53)	1.82 (1.34 to 2.46)	1.65 (1.10 to 2.46)
Age in years	0.83 (0.78 to 0.88)	0.92 (0.87 to 0.97)	0.99 (0.93 to 1.06)
Preterm birth	1.65 (1.24 to 2.20)	1.46 (1.08 to 2.00)	1.38 (0.95 to 1.99)
Paternal asthma	1.43 (0.96 to 2.12)	1.71 (1.13 to 2.58)	1.25 (0.75 to 2.08)
Sex (boy)	0.83 (0.67 to 1.03)	0.79 (0.63 to 1.00)	0.91 (0.69 to 1.19)
Father works in dusty environment	1.15 (0.90 to 1.48)	1.64 (1.27 to 2.12)	1.13 (0.82 to 1.55)
Unemployed mother	1.31 (1.01 to 1.68)	1.28 (0.97 to 1.68)	1.11 (0.80 to 1.55)
School in area of increased dust pollution	1.46 (1.14 to 1.87)	1.22 (0.93 to 1.60)	1.28 (0.93 to 1.78)
Damp home	1.56 (1.19 to 2.04)	1.24 (0.92 to 1.62)	1.25 (0.88 to 1.78)
Rented accommodation	1.32 (1.08 to 1.60)	1.08 (0.83 to 1.39)	0.88 (0.64 to 1.21)

School absenteeism for respiratory symptoms is a useful indicator of respiratory morbidity.[3 6 11] Absences from school (for more than six days) due to respiratory symptoms and admissions to hospital for the same reason declined slightly between 1991 and 1993.

RISK FACTORS FOR SYMPTOM PROFILES

Reports of the effects of parental smoking on lung function and respiratory health of children are inconsistent. There are reports of strong associations of childhood respiratory symptoms with passive smoking especially in susceptible children,[12 13] and suggestions that the findings may be dependent on the amount of contact between parent and child,[14] or whether the mother smoked during pregnancy.[15 16] We have been unable to replicate these findings in 1993 despite the large numbers in the study and controlling directly for many social class and environmental factors. Neither was there an association between having been breast fed and later childhood respiratory symptoms, which is in agreement with other recent reports.[17 18] Reported wheeze has been shown to be more likely with the reported presence of dampness in the home,[19] our study supports this. Babies born preterm were more likely to develop the symptom triad during childhood than babies born full term.[20]

There are significant detrimental effects of air pollution on respiratory health.[21–24] In asthmatic children an increase in the severity, but not the prevalence, of respiratory symptoms has been associated with air pollution.[25] Other surveys have reported cough as the main respiratory symptom associated with high levels of air pollution.[6 25–29]

Our earlier report showed that excess cough as a single symptom was associated with particulate air pollution, and the more sophisticated analysis in this paper confirms that observation. However, the single symptom of wheezing and the symptom triad of cough, wheeze, and breathlessness did not correlate with pollution. The symptom triad correlates best with the features of atopy and also with having been born prematurely. The difference in risk profiles between cough alone and the triad of cough, wheeze, and breathlessness are consistent whether the data are analysed by simple univariate comparisons or multiple logistic regression, which suggests that these epidemiological classifications may represent distinct clinical entities. Thus, if a child has cough, wheeze, and breathlessness, then a diagnosis of asthma seems very probable, and conversely the single symptom of excess cough could be a non-specific response to adverse environmental conditions and not represent asthma at all. Such a hypothesis cannot be answered from cross sectional studies alone but there is a further observation that supports it.

Doctor diagnosed asthma was reported in 83 and 90% of children with the symptom triad in 1991 and 1993 against only 10 and 23% of those with excess cough only and hardly at all in asymptomatic children. Treatment prescribing follows a similar pattern. Thus doctors appear to have recognised a similar distinction in clinical practice.

Between 1991 and 1993 there was a significant increase in the prevalence of doctor diagnosed asthma and also in the number of children receiving medication for asthma. Since overall symptom prevalence was unchanged, this suggests a change in medical behaviour. The increase in labelling was most marked in those reporting the single symptom 'excess cough', with more than twice as many of these children being diagnosed as asthmatic and, if allowance is made for the non-asthma medication being unchanged, nearly twice as many received asthma therapy. In 1993, one in eight children that doctors had diagnosed as asthmatic had been diagnosed on the basis of the single symptom of cough. Whether these children really have asthma warranting treatment or whether doctors have become more aware of, and aggressive towards, cough as a marker of asthma remains unknown. Possibly doctors use cough together with auscultation of the chest to reach a diagnosis. If the index of asthma in our survey had been 'doctor diagnosis of asthma' we would be reporting an increase in asthma of nearly 5% over 2 years, which, since overall symptom prevalence was unchanged, would have been misleading.

In conclusion, we hypothesise that the symptom triad of cough, wheeze, and breathlessness occurring in a child may be a better marker of true asthma in epidemiological surveys than relying on either single symptoms or doctor diagnostic patterns. Since asthma prevalence is so dependent on the definition adopted, further studies are needed either to confirm this hypothesis or produce a better version that can be adopted as a standard.

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